

VOLUME 3

# ARCHIVES OF PATHOLOGY

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## PATHOLOGIC ANATOMY OF "ATYPICAL PNEUMONIA, ETIOLOGY UNDETERMINED"

ACUTE INTERSTITIAL PNEUMONITIS

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During the years 1940 to 1944 it became possible for the central pathologic laboratory of the United States Army, Institute of Pathology of the Army Medical Museum, to collect 90 cases of "atypical pneumonia, etiology undetermined" in which postmortem examinations were made. It is the purpose of this paper to analyze the morbid anatomic changes in the 42 cases of that series which are susceptible of analysis, i.e., those in which the case histories and autopsy protocols are reasonably complete and enough tissue is available for an unequivocal estimate of the pathologic process. It should be stressed that this accumulation of cases with autopsy reports became possible only through the efforts of medical officers in the field.

Pathologically, all of the cases acceptable for this report were cases of acute interstitial pneumonitis, a designation which I propose to use for the remainder of this discussion rather than the clinical designation of "atypical pneumonia, etiology undetermined." The pathologic processes seen in the lungs of patients dying of this disease in this country and abroad during the four year period of study were fundamentally alike. A small number of civilian autopsy cases in this country were compared with those arising in military areas, without any pathologic differences being noted. Similarly, while most of the patients were young adults, a few were infants or children and a few were older persons, and they too presented no essential anatomic differences. Therefore, for purposes of clarity and general description, the lesions will be described in their entirety before taking up specific cases.

### MORBID ANATOMY

In a number of instances portions of the lungs at autopsy showed frank bronchopneumonia and only occasionally lobar pneumonia, as well as areas of acute interstitial pneumonitis. The reasons for believing that such lobular or lobar pneumonia represented secondary bacterial in-

fection superimposed on primary acute interstitial pneumonitis will be brought out in later paragraphs. The primary and secondary infections were impossible to disentangle in a number of cases, and these are not included in this series.

The following composite description is based on 21 cases in which multiple sections of lung revealed only acute interstitial pneumonitis. Grossly, such lungs varied in weight from moderately heavier than normal to normal. The weights of lungs are exceedingly difficult to estimate. Miller,<sup>1</sup> whose normal values I have accepted, stated the weight of the right lung as between 500 and 550 Gm. and that of the left as between 425 and 490 Gm. The weights of the lungs of 10 adults in my series, a sample of the whole, ranged from 460 to about 1,000 Gm. In general, the greater weights were associated with large zones of edema or hemorrhage (see later description) or with marked congestion. The pleural surfaces were smooth and glistening, but occasionally patches of frank fibrinous exudate were detected, usually only in extremely small quantities. A pleural effusion of clear amber fluid in small to moderate quantities was seen only a few times. On section, such lungs showed the following characteristic picture: The extent of involvement of the parenchyma was variable. A spread through a portion of one lobe, a whole lobe or a whole lung or diffuse bilateral spread were the degrees encountered (fig. 1). The lesions were focal, with a gross resemblance to miliary granuloma. On closer inspection, however, the slightly raised whitish nodules were found to be thickened bronchiolar walls, from the center of which frank pus either exuded spontaneously or appeared on slight pressure. The immediately surrounding lung tissue was either spongy and grossly normal or was somewhat edematous, occasionally hemorrhagic, and always congested. The number of involved bronchioles varied considerably, the involvement ranging from a spotty distribution to one includ-

From the Institute of Pathology, Army Medical Museum, Washington, D. C.

1. Miller, W. S.: *The Lung*, Springfield, Ill., Charles C Thomas, Publisher, 1937.

ing every bronchiole on the cut surface. The larger branches of the tracheobronchial tree were described as normal or as lined by a slightly edematous and somewhat congested mucous membrane, rarely acutely inflamed and ulcerated. The fluid found within the lumens of such branches was either scanty, mucoid and clear

plasma cells, occasional polymorphonuclear leukocytes and eosinophils were present in the edematous submucosa (fig. 2). Elastic tissue stains and reticulum stains showed no abnormalities. The cartilaginous plates showed no lesions. Sections taken from the affected portions of the lung showed a spotty distribution of involved bron-

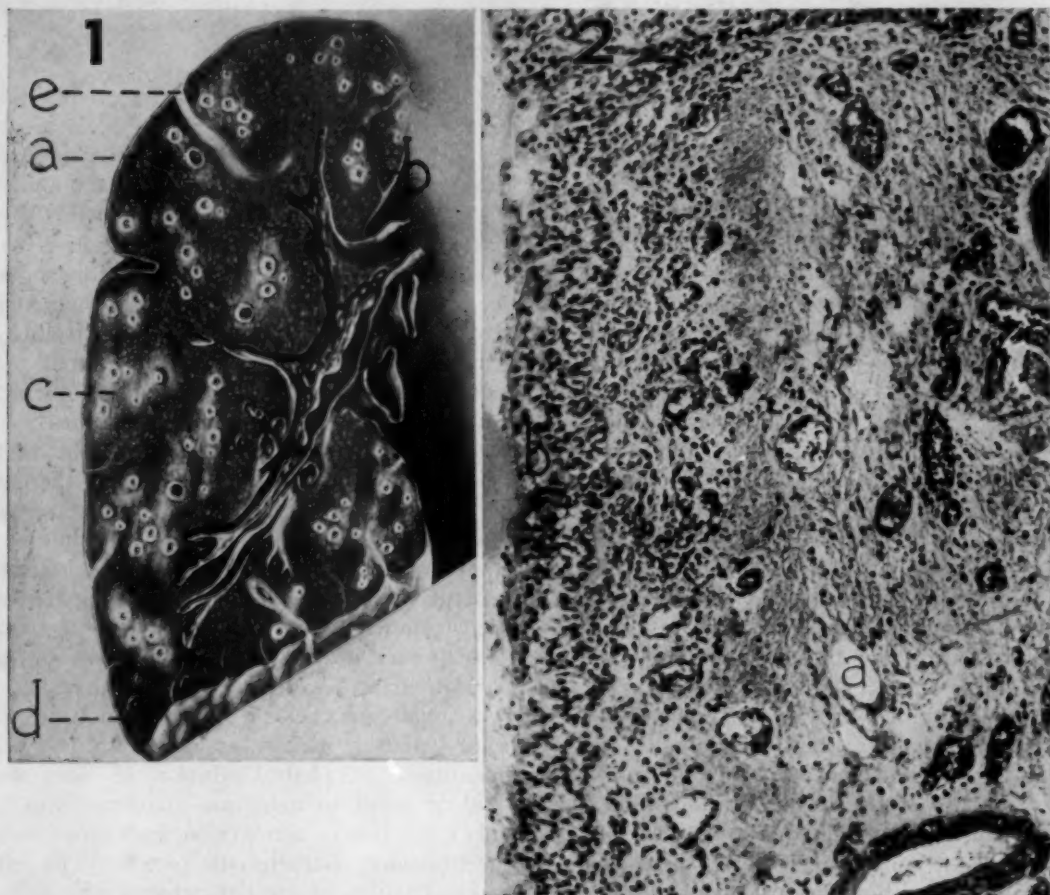


Fig. 1.—Negative 80921. Accession 91654. Drawing, reduced, of a hemisection of a lung in a case of acute interstitial pneumonitis. The peribronchial and peribronchiolar thickening is seen in its widespread form in this hemisection. Some branches of the bronchial tree can be seen exuding pus from their lumens (*a*), while others show plugs of pus or inspissated contents (*b*). Around some bronchioles there is slight consolidation (*c*) while the intervening patches of lung tissue are air containing (*d*). Edematous septums are seen at *e*.

Fig. 2.—Negative 74286. Accession 85380.  $\times 150$ . Section of a major bronchus, in which the most conspicuous change is edema, congestion and round cell infiltration in the submucosa (*a*). The mucosa (*b*) is not altered.

or somewhat more abundant and seromucoid, rarely blood tinged, sometimes purulent.

Microscopic sections of the larger and medium-sized branches of the bronchial tree showed intact mucous membrane with marked submucosal edema and congestion. In only 2 instances was focal ulceration observed. A scattering of large mononuclear cells, lymphocytes, small numbers of

chioles as a rule. Inflamed bronchioles sometimes alternated with microscopically normal ones. The most characteristic lesion consisted of frank pus, desquamated cells of the mucous membrane, cellular debris and mucoid fluid in the bronchiolar lumens (figs. 3 to 6). Frequently an air bubble was trapped in the midst of this cellular mass (fig. 3). Ulceration of the

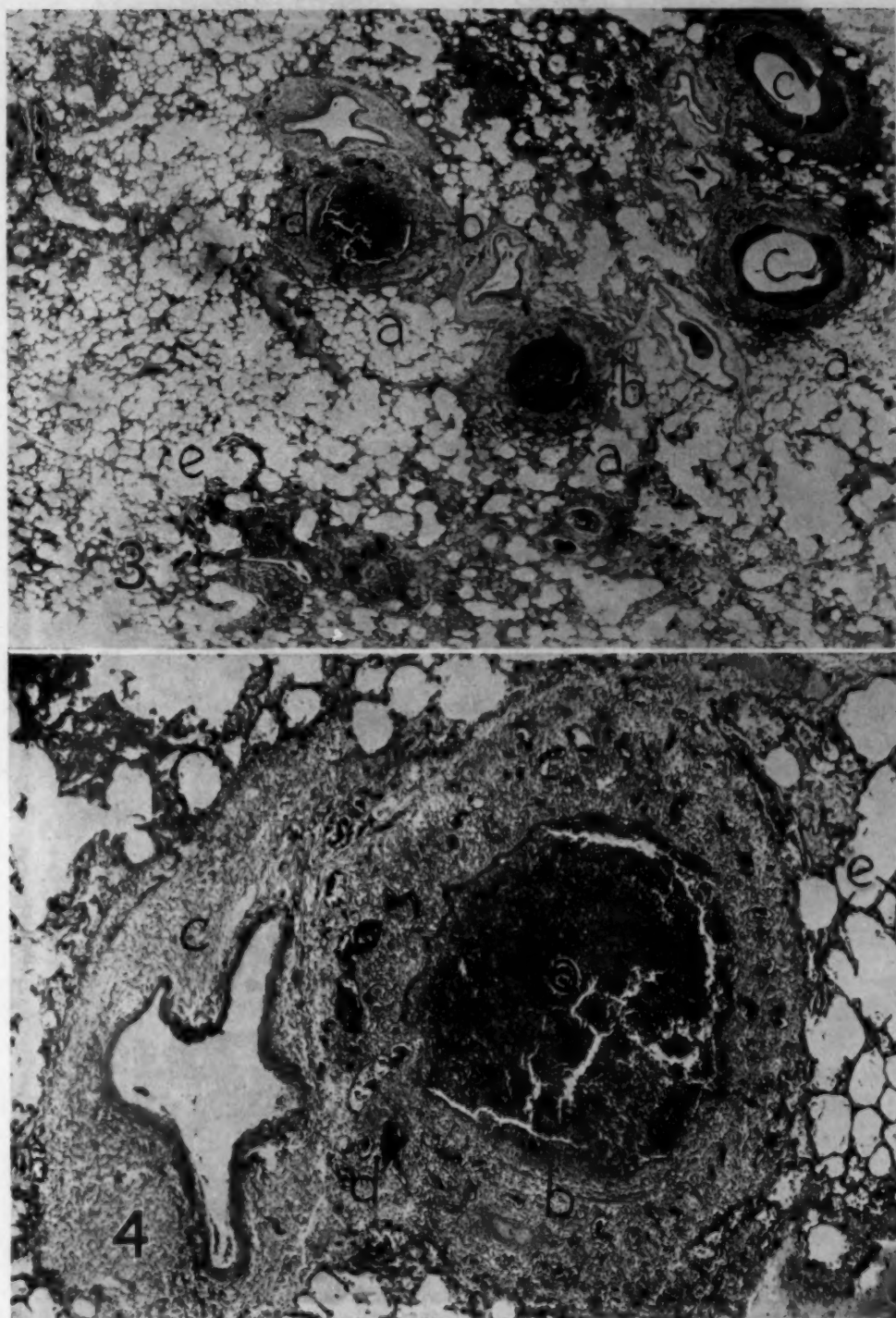


Fig. 3 (case 15).—Negative 80618. Accession 96956.  $\times 9$ . Note the discrete involvement of bronchioles (a). Some lumens are filled with pus (b). Some lumens show trapped air bubbles (c). There are peribronchiolar edema and round cell infiltration at d. Note that most of the alveolar sacs are air containing (e).

Fig. 4 (case 15).—Negative 81217. Accession 96956.  $\times 27$ . Higher power magnification of a single bronchiole (a) shown in figure 3. Note the edema and round cell infiltration of the wall (b), the septal edema (c) and the congestion (d). The thickening of the alveolar wall by round cell infiltration can be seen at e.

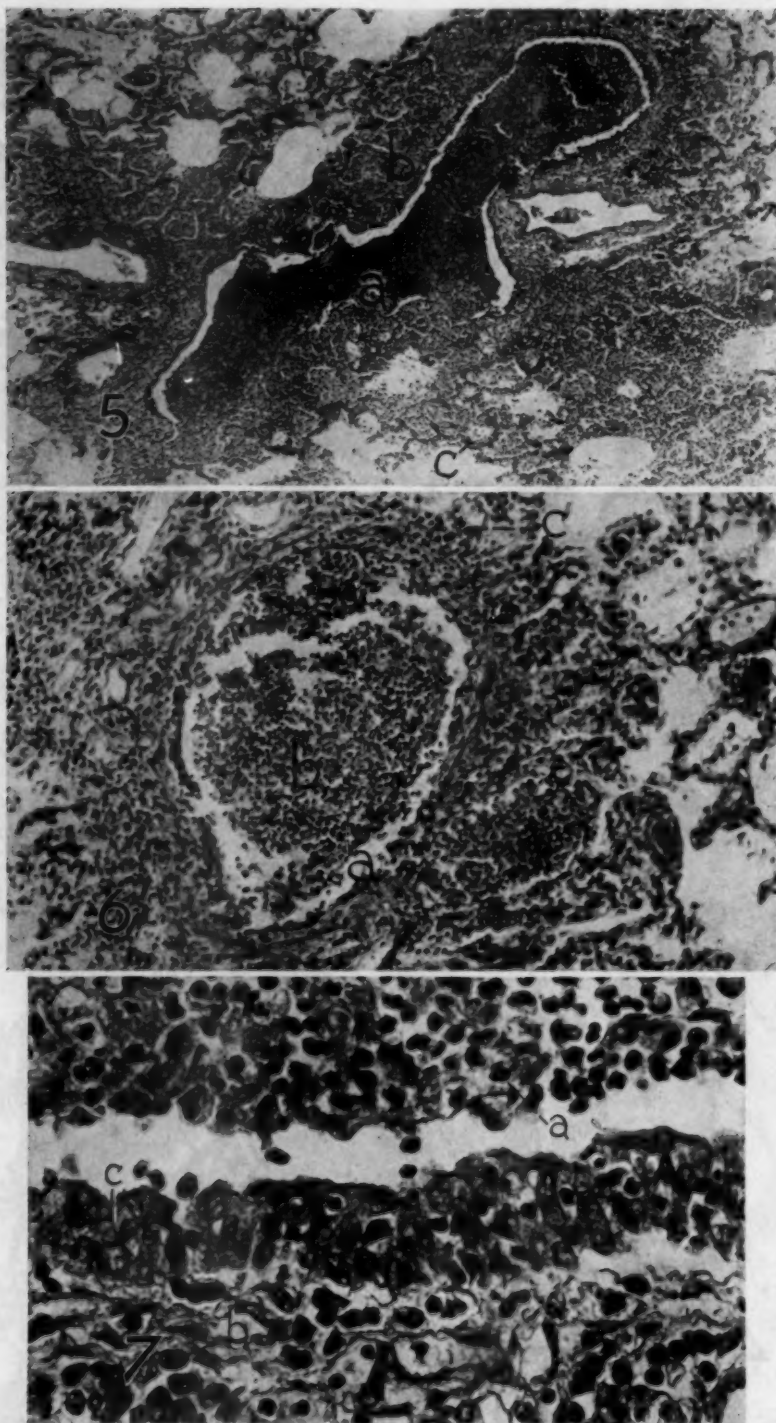


Fig. 5.—Negative 74279. Accession 85380.  $\times 88$ . There is partial ulceration of this bronchiole (a), the lumen of which is filled with pus. The peribronchial round cell exudate (b) extends regionally into alveolar walls (c), thickening them.

Fig. 6.—Negative 74282. Accession 79032.  $\times 132$ . A partially ulcerated bronchiole (a) shows a lumen filled with polymorphonuclear leukocytes and sloughed mucosal lining cells (b). The wall is densely infiltrated with round cells (c).

Fig. 7.—Negative 80912. Accession 79032.  $\times 454$ . High power view of an inflamed bronchiole, showing the contrast between polymorphonuclear leukocytes and epithelial debris in the lumen (a) and the predominantly plasma cell infiltration in the wall (b). The mucosa is shown at c.

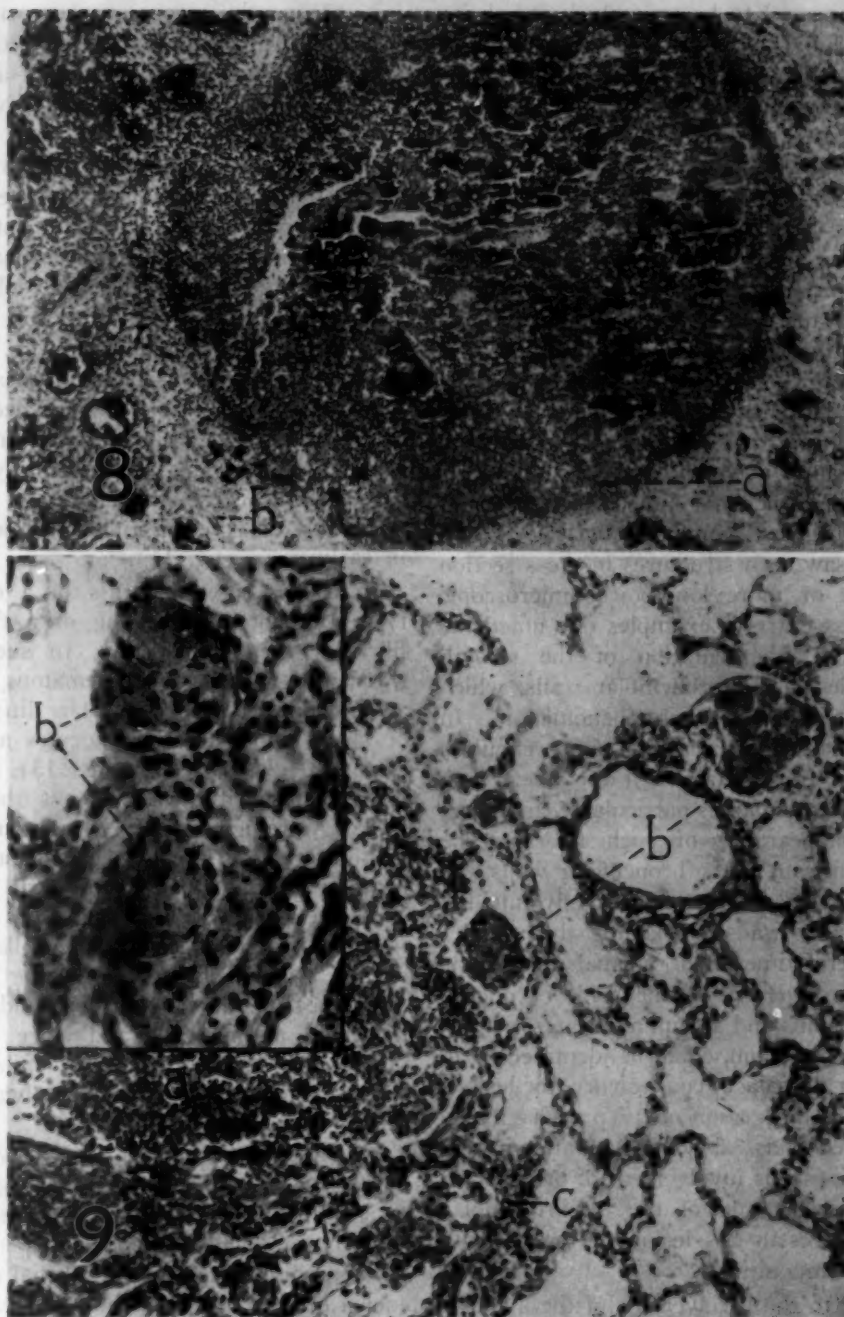


Fig. 8 (case 15).—Negative 80614. Accession 96956.  $\times 85$ . Occasionally one sees a bronchiole so completely transformed as to resemble an abscess (a). The mucosa is completely gone. It is recognizable as a bronchiole only by the accessory bronchiolar structures, such as bits of smooth muscle in the wall (b). Note the extreme dilatation of this bronchiole, which covers more than a low power microscopic field.

Fig. 9.—Negative 80916. Accession 79032.  $\times 120$  (insert  $\times 230$ ). An inflamed bronchiole is seen at a. Alveolar lumens filled with hyaline balls are present at b. Note the mononuclear exudate in the alveolar wall (c) and the freedom of the alveolar spaces from polymorphonuclear leukocytic exudation.

bronchioles was present fairly uniformly and quite characteristically throughout this series of cases. It appeared to be an early lesion, being seen in the lungs of patients who were ill for only a few days prior to death. In some instances, the entire bronchiolar mucous membrane was desquamated, and the bronchioles could be recognized only by the smooth muscle content of the wall surrounding what appeared to be a frank abscess (fig. 8). In other instances, only a portion was ulcerated, the remainder being either intact or in variable stages of disintegration (figs. 5 and 6). The affected bronchial walls and peribronchial tissues were moderately to markedly thickened by a dense exudate of plasma cells, lymphocytes, large monocytes and edema fluid (figs. 6 and 7). Note the contrast to the predominantly polymorphonuclear leukocytic exudate of the bronchiolar lumens. Dilatation of such bronchioles was common (fig. 8). Occasionally one saw such structures in cross section covering one or more low power microscopic fields. In less extreme examples one noted the separation and fragmentation of the smooth muscle bundles of the bronchiolar walls, which was interpreted as a stretch phenomenon. In such cases elastic tissue stains and reticulum stains showed fragmentation of the fibers and, underlying ulcerated areas particularly, an almost complete disappearance of such fibers. The round cell infiltrate of the bronchiolar walls and peribronchial areas extended radially into the adjacent alveolar walls, thickening them sometimes to several times their normal dimensions (fig. 10). Involvement of the walls of ductuli alveolares, atriums and sacculi alveolares, as well as of alveoli pulmonum, could be identified in all sections. For the sake of convenience, the lesions affecting the distal portion of the primary lobule will be referred to as "alveolar" hereafter in this discussion. It is this involvement of bronchiolar and alveolar walls and of the peribronchial areas which gives to this lesion the name acute *interstitial* pneumonitis.

In contrast to the involvement of the alveolar walls, which tended to be most severe close to the affected bronchioles, the alveolar lumens were frequently of normal dimensions and air containing. Elastic tissue stains brought out the occasional fragmentation of fibers in alveolar walls, but as a rule rupture or necrosis was not seen. The contents of the alveoli were subject to much variation even in the same case when different parts of the lung were examined. The most frequent abnormality was extensive desquamation of alveolar lining cells (which must be dis-

tinguished from exudation of mononuclear cells). Focal areas of atelectasis were also common. Less frequently, serous exudate with and without the formation of hyaline membrane was noted. In such areas absence of an admixture of polymorphonuclear leukocytes was the rule (fig. 11). Hemorrhages, usually unorganized and apparently terminal, when present within alveoli tended to be limited to those alveoli close to involved bronchioles. A not infrequent feature was masses of fibrin, occasionally seen undergoing organization, filling alveoli and taking their shape. Leukocytic admixture in such fibrinous masses was not the rule (fig. 9). Lastly, there were also areas of metaplasia of alveolar lining cells to a single row of deeply staining columnar cells or focal or diffuse metaplasia to squamous cells (fig. 15). Similarly, metaplasia to squamous cells, either focal or diffuse, was commonly observed in inflamed bronchioles even in early cases (fig. 14).

In a few cases pleuritis of a characteristic type was noted, consisting of a thin layer of fibrin without leukocytes. In such cases the subpleural tissues were edematous and moderately congested and showed a diffuse infiltrate of large monocytes, lymphocytes and in lesser numbers, plasma cells (fig. 13). Where no fibrinous pleuritis was present the subpleural tissues were normal. The pulmonary septums in the involved areas were edematous, sometimes markedly so, and this was recognizable grossly (figs. 1 and 12). Not only were separation and fragmentation of the collagenous connective tissues noted, but in the edema fluid there was a moderately dense round cell exudate in which plasma cells and large mononuclear phagocytes predominated. Lymphatics within such affected areas were almost always markedly dilated (fig. 12).

The regional lymph nodes were slightly to moderately hemorrhagic and edematous but in no instance showed acute suppurative lymphadenitis. Follicular lymphoid hyperplasia, moderate swelling of reticuloendothelial elements and edema of the pulp were the chief features of the draining lymph nodes.

In the grossly unaffected portions of the lung, no departures from the normal were observed microscopically. In a few instances in which the diaphragm was available for study, individual muscle fibers showed hyaline degeneration. The spleen showed no abnormalities in any case of this series. The bone marrow appeared unaffected. (Note: These are the observations in uncomplicated interstitial pneumonitis.) The changes in the central nervous system will be

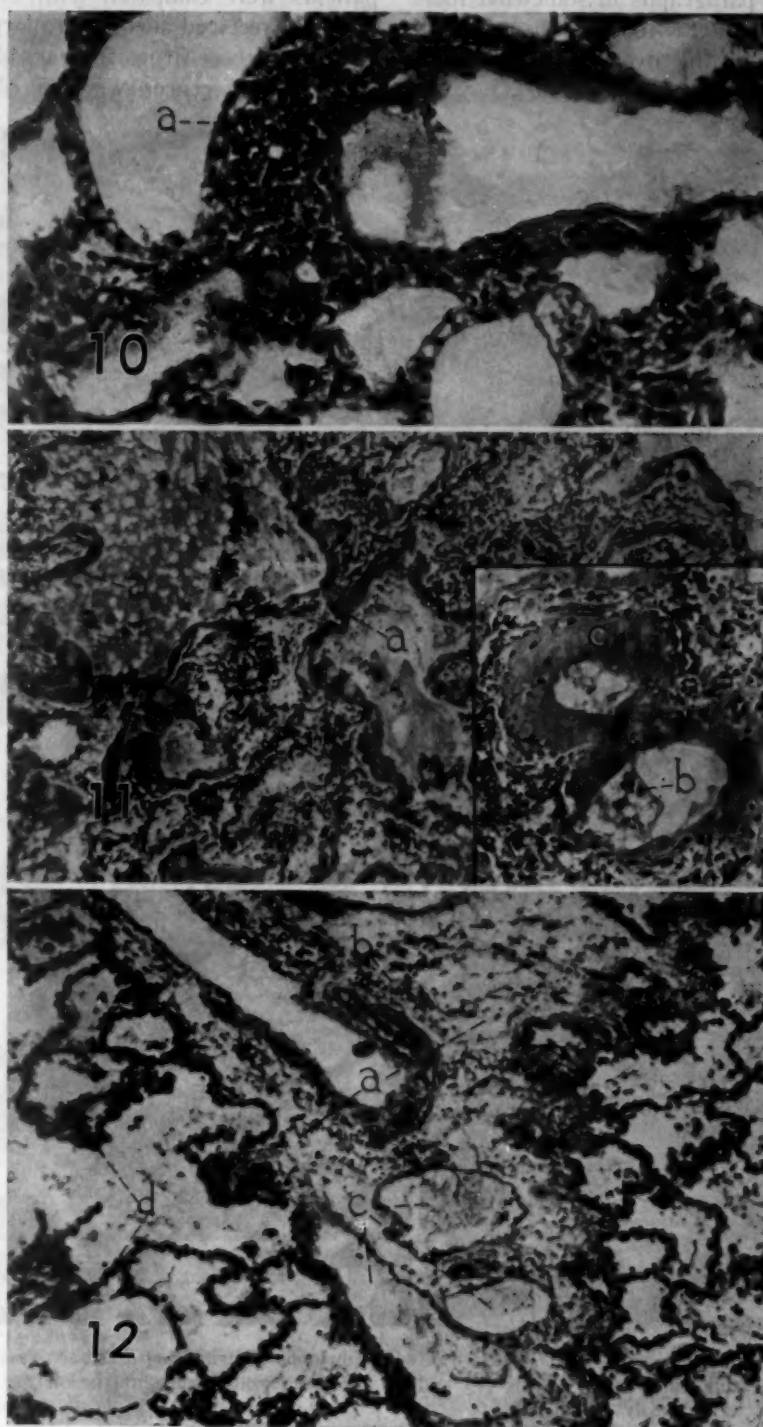


Fig. 10.—Negative 74285. Accession 79032.  $\times 285.5$ . The interstitial nature of the round cell infiltrate is particularly well shown at *a*, a greatly thickened alveolar wall.

Fig. 11 (case 4).—Negative 80593. Accession 71380.  $\times 114$  (insert  $\times 143$ ). Hyaline membranes adherent to alveolar walls are well shown at *a*. Their formation from serous exudate is suggested at *b*, where the centers appear more fluid than the periphery (*c*).

Fig. 12 (case 5).—Negative 80623. Accession 81392.  $\times 138$ . Septal edema (*a*) and diffuse round cell infiltration (*b*) are shown, as well as marked lymphangiectasis (*c*). Note that the alveolar walls are diffusely thickened by their round cell content (*d*).

taken up in later paragraphs in somewhat more detail; they were chiefly those of hemorrhagic encephalopathy. In the liver occasional small focal necroses were observed.

patients were compared with those of patients who had received adequate to large doses of one or both of these drugs for variable periods. No anatomic differences were noted in these two

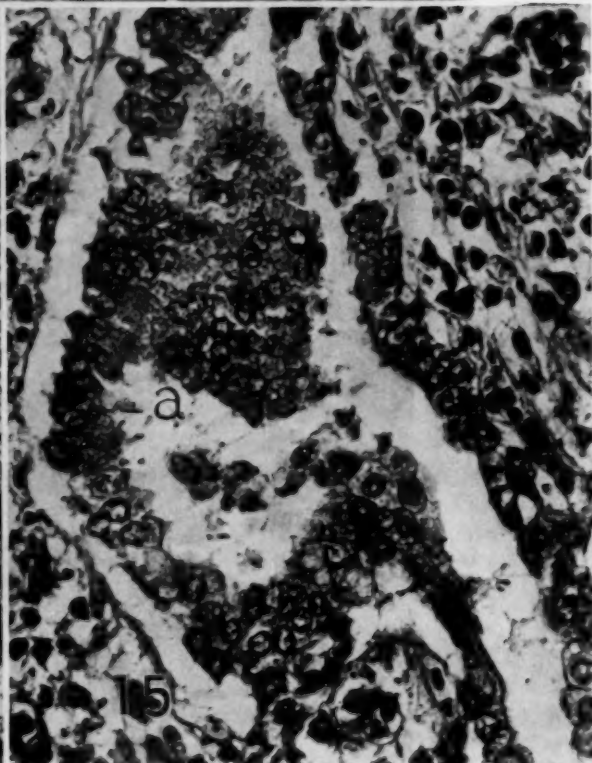
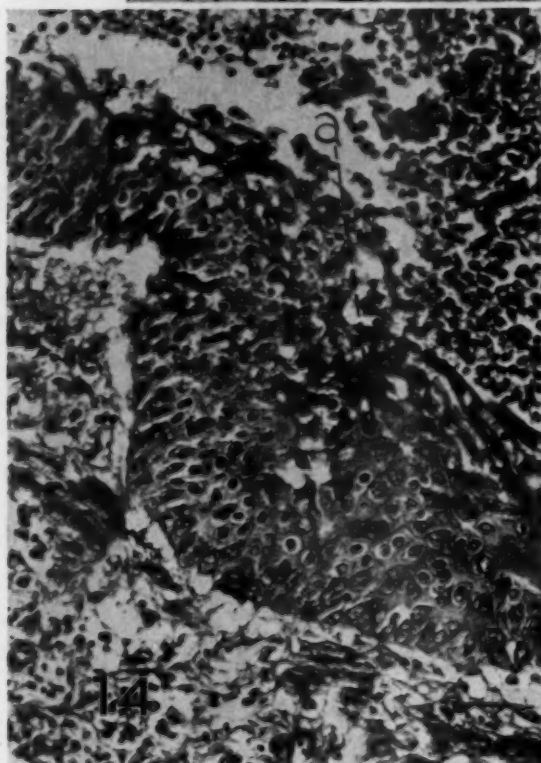
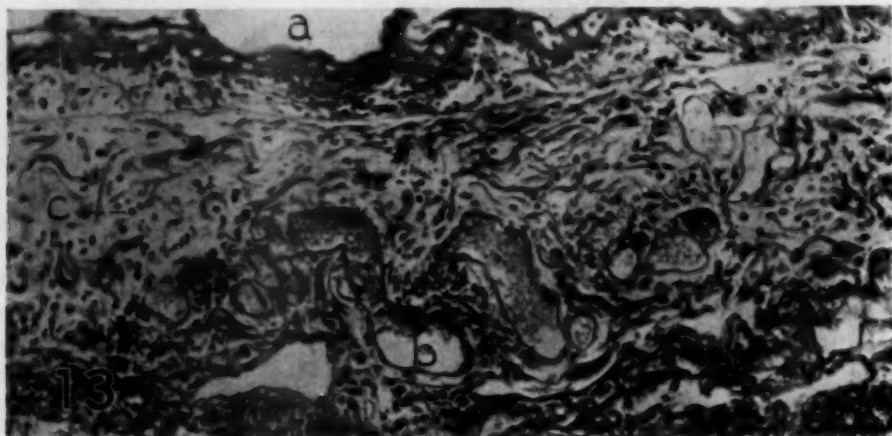


Fig. 13.—Negative 74281. Accession 79032.  $\times 144$ . Fibrinous pleuritis (a) was seen in a few cases. Note the congestion of the subpleural blood vessels (b) and the scattered round cell infiltration (c). Polymorphonuclear leukocytes are conspicuously absent.

Fig. 14 (case 14).—Negative 80682. Accession 91645.  $\times 221$ . Metaplasia was a fairly common change in this series. A focus of squamous cell metaplasia (a) is seen in a bronchiole.

Fig. 15 (case 4).—Negative 80592. Accession 71380.  $\times 480$ . A focus of columnar cell metaplasia (a) is seen lining an alveolus.

A search for inclusion bodies in sections of lungs stained with hematoxylin and eosin and Giemsa stains revealed none. A number of patients received neither sulfonamide drugs nor penicillin, and the pulmonary lesions of these

groups of patients, i. e., drug-treated and non-drug-treated ones. The non-drug-treated patients of this series represent patients who were moribund when admitted and who died shortly thereafter (examples are Army Medical Museum

accessions 81392 and 72095 [cases 5 and 10 in this paper]). This is not meant to imply that these drugs are ineffective therapeutically, on which I have no opinion, but is meant to stress merely the lack of anatomic change induced by such therapy.

A survey of multiple lung tissue sections was made in order to evaluate the bacterial flora in the affected lungs. MacCallum stains, toluidine blue and the Brown-Brenn method were used. The observations in several cases, a sample of the whole, may be summarized as follows (Army Medical Museum accession numbers are used to identify the cases):

In cases 1, 2 and 3 (77526, 108472, 70891) one observed good examples of pure acute interstitial pneumonitis. In case 1 several sections of lung showed no organisms whatsoever. In case 2 two sections of five examined showed occasional gram-positive cocci in pairs, in small chains and occasionally in clusters, confined to the bronchiolar lumens containing pus. None were seen in alveolar walls, alveolar lumens, bronchiolar walls or septums. In case 3 only one section showed a few encapsulated gram-positive diplococci confined to a few bronchiolar lumens.

Case 4 (71380) was one of pure acute interstitial pneumonitis in which hyaline membrane formation was a conspicuous feature and in which there was fibrinous pleuritis. No organisms were found anywhere in several sections examined.

Case 5 (81392) was one of pure acute interstitial pneumonitis in which there was marked and widespread infiltration of alveolar walls, by mononuclear cells. No organisms were found.

In cases 6 and 7 (97140, 75846), in addition to the interstitial changes in the lungs, there were fairly widespread edema and hemorrhage in alveolar lumens. No bacteria of any kind were found in the several sections examined. Case 7 is reported in detail on this page.

In case 8 (96956) great bronchiolar dilatation was a conspicuous feature of the acute interstitial pneumonitis. No organisms were found in thickened alveolar walls or in alveolar spaces, but in the greatly dilated bronchiolar lumens, mixed in with the purulent exudate, were scanty numbers of organisms. A single staphylococcal cluster was seen in one bronchiolar lumen, and in other bronchioles there were occasional gram-positive cocci in short chains and in pairs also confined to the lumens. There were hemorrhagic lesions in the brain (see detailed report of case 8, page 196). Multiple sections of the brain failed to reveal organisms of any kind.

Case 9 (109313) was another case of acute interstitial pneumonitis and hemorrhagic encephalopathy. In the lung sections an occasional gram-positive chain of cocci was found in the bronchiolar exudate but in no other place. No organisms were seen in the hemorrhagic foci or elsewhere in the sections of the brain.

In case 10 (72095) portions of the lungs showed acute interstitial pneumonitis, other areas showed a lobular pneumonia, while still others showed a mixture of the two pathologic processes. No organisms were seen in the area showing only acute interstitial pneumonitis. In the zones of lobular consolidation a mixed bacterial flora was found in bronchiolar lumens, in bronchiolar walls and in the alveolar exudate. The following organisms could be identified in fairly large numbers: minute gram-negative bacilli, minute gram-

positive cocci in pairs and large gram-negative bacilli with rounded ends. The pathologic process and the mixed bacterial types were suggestive of an aspiration type of pneumonia superimposed on acute interstitial pneumonitis.

Cases 11 and 12 (109939, 87961) were instances of acute interstitial pneumonitis complicated by abscess formation. The findings in case 12 are summarized on pages 197 and 198. In case 11 many lung sections showed no organisms whatsoever in the areas of acute interstitial pneumonitis, while large numbers of gram-positive cocci in staphylococcal clusters were seen in the abscess areas. Furthermore, around the abscess areas there were zones of lobular consolidation, and there, too, staphylococcal clusters were identified with ease in the alveolar exudate and in bronchiolar lumens and walls.

#### REPORT OF CASES

The following cases were selected for the demonstration of specific points.

**CASE 7 (75846).**—A 26 year old white man was admitted to his station hospital in coma. There were moist rales in the apex of the left lung, and the patient was cyanotic. The roentgenologic report stated that there was slight density at the apex of the left lung. The temperature on admission was 104 F.; on the second hospital day it had risen to 106 F. The leukocyte count on admission was 7,500 white blood cells per cubic millimeter, of which polymorphonuclear leukocytes were 55 per cent, lymphocytes 42 per cent and monocytes 3 per cent. No sputum was obtained. Because of the cyanosis and a rapid pulse rate, the patient was placed in an oxygen tent, and sulfathiazole therapy was started. The next day the respirations were labored, the pulse fast, and there was deepening cyanosis. The patient died on the next day with a convulsive seizure and a lapse into deeper coma.

At autopsy the lungs were described as "heavier than usual," with marked congestion and widespread patchy hemorrhages. On inspection the blocks of wet tissue submitted showed frank peribronchiolar whitish thickenings spread diffusely through markedly congested lung tissue.

Cultures of blood taken at autopsy remained sterile after sixty hours. Smears from the lungs showed no bacteria. Cultures of lung tissue showed only rare colonies of *Staphylococcus aureus* and *Bacillus coli*. Stained sections of the lung showed no bacteria.

Microscopic examination of the lungs showed acute interstitial pneumonitis characterized by marked ulcerative acute bronchiolitis and marked round cell infiltration of bronchiolar and alveolar walls. The alveolar lumens either were air containing or showed massive desquamation of alveolar lining cells, serous exudation or recent hemorrhage. Small numbers of alveoli contained scattered monocytes and lymphocytes. Polymorphonuclear leukocytes were not found in any appreciable numbers outside of bronchiolar lumens. Occasional alveolar hyaline membranes were seen. Congestion of all the blood vessels, including the alveolar capillary bed, was conspicuous.

The other organs examined showed no significant changes grossly or microscopically. The brain was not examined.

Attempts to isolate a virus by inoculation of filtrates from lung tissue into mice, guinea pigs and hamsters were unsuccessful. It should be emphasized that post mortem ordinary bacteriologic methods re-

vealed no significant organisms in the lung, and none were seen in appropriately stained tissue sections.

**CASE 13 (91645).**—A reputedly successful attempt at isolation of the virus from the lungs was made in this case. Dr. Monroe D. Eaton, of the Board for the Investigation of Influenza and Other Epidemic Diseases, United States Army, supplied the factual data on the viral studies.

A 24 year old white man entered the hospital with a history of an infection of the upper respiratory tract of four days' duration, for which he was treated on sick call for three days with "nose drops and pills." On the day of admission he felt feverish, had generalized muscular pains, pain in the anterior part of the chest and cough. The respiratory movements were equal but shallow; there was slight dullness at the bases of both lungs, as well as many fine moist rales throughout both lung fields, more marked at the bases.

On the second day in the hospital there was a sudden rise of the temperature with increasing dyspnea. A roentgenogram of the chest showed diffuse bilateral "miliary" mottling. Oxygen therapy and an adequate sulfadiazine level in the blood produced no clinical improvement. He died that day, the sixth day of his illness.

The initial blood count was reported as 8,000 white blood cells with a "normal differential" count; four days later the count was 16,600 white blood cells with no significant change in the differential count.

No typable pneumococci could be isolated from the sputum.

At autopsy the essential pathologic changes were limited to the lungs. The right lung weighed 1,085 Gm., and the left, 945 Gm. The bronchi contained abundant yellowish, purulent, frothy exudate. The pleural surfaces were smooth. On section, both lungs were infiltrated extensively and diffusely by whitish peribronchiolar nodules, up to 1 cm. in diameter, with confluent nodules measuring up to 4 cm. in diameter. The centers of these nodules contained plugs of pus.

Postmortem cultures of lung tissue revealed no growth in seventy-two hours. Filtrates of lung tissue were inoculated intranasally into cotton rats by Dr. Monroe D. Eaton, who stated that about 50 per cent of the animals had pulmonary lesions like those described in his report.<sup>18</sup> He stated further that virus from this case produced pulmonary lesions consistently in hamsters and cotton rats after being passed through 30 chick embryos.

Microscopic examination of the lung tissue showed extensive bilateral acute interstitial pneumonitis with almost uniform bronchiolar ulceration. A varied alveolar exudate was found, ranging from desquamated lining cells to edema fluid, fibrinous exudate, hemorrhage and hyaline membrane formation. Patches of polymorphonuclear exudate in alveolar lumens seemed to be derived by direct extension from involved bronchioles. There were occasional foci of necrosis of alveolar walls. Acute bronchiolitis with marked dilatation was widespread; foci of metaplasia to squamous cells were common (fig. 14). The thick collars of round cells around the bronchioles, extended widely into alveolar walls, thickening them markedly.

Numerous tissue sections stained for bacteria revealed none even in the bronchiolar lumens.

Pathologically, these lungs showed the most intense involvement of any in this series.

**CASE 8 (96956).**—This was a case in which hemorrhagic encephalopathy occurred.

1a. Eaton, M. D.; Meiklejohn, G.; Van Herick, W., and Talbot, J. C.: *Science* 96:518, 1942.

A 28 year old white man was admitted to the hospital complaining of cough and pains in the chest following a "cold" of several days' duration. There were moist rales in the right side of the chest, and the radiologist reported "peribronchial pneumonia spreading from the right hilus into the upper lobe." The temperature was 101 F. on admission and reached 105 F. in the next two days. The leukocyte count on admission was 8,850, of which polymorphonuclear leukocytes were 78 per cent and lymphocytes 21 per cent. The sputum was "thick and bloody." Because of slight cyanosis, the patient was placed in an oxygen tent. The pulse rate rose steadily and dyspnea progressively increased up to the fifth day in the hospital. Sulfadiazine and oxygen therapy were unavailing. The patient lapsed into a semicomatose state and died on that day.

At autopsy the significant pathologic changes were limited to the lungs and the brain. The right lung was not weighed; the left weighed 700 Gm. The right lung showed patches of atelectasis and marked congestion, and on section there were many thickened small bronchi and bronchioles, the lumens of which exuded thick pus. Around the involved bronchioles the lung tissue was hemorrhagic or hyperemic, with patches of aerated lung tissue between such involved areas. The interlobular septums were widened and hemorrhagic.

TABLE 1.—Summary of Findings in a Postmortem Bacteriologic Study Made in Case 8

	Blood Agar, Aerobic	Peptic Digest, Aerobic Blood Agar, CO <sub>2</sub>	Chocolate Agar, CO <sub>2</sub>
Trachea	55 colonies, alpha type of streptococcus 150 colonies, Staph. aureus		
Bronchi	65 colonies, alpha type of streptococcus 20 colonies, Staph. aureus	Similar qualitative findings	Similar findings
Rt. lung	No growth		6 colonies, alpha type of streptococcus
Lt. lung	1 colony, Staph. aureus		No growth

The brain weighed 1,560 Gm. The only abnormalities noted consisted of fine perivascular hemorrhages mainly in the white matter throughout the cerebral hemispheres but most marked in the corpus callosum.

The laboratories of the Respiratory Disease Commission of the Board for the Investigation and Control of Influenza and Other Epidemic Diseases, United States Army, furnished the accompanying summary of their findings in a postmortem bacteriologic study (table 1).

Microscopically, the lung sections showed acute interstitial pneumonitis. The most pronounced changes were seen in the bronchial tree. The larger bronchi showed shallow ulcers of the mucous membrane covered by a thick fibrinopurulent exudate. The smaller branches and the bronchioles had lumens filled with pus. Microscopically, there were ulceration of the mucosa and marked round cell infiltration of the peribronchiolar areas and of the alveolar walls. The alveolar contents were variable. In some places the alveoli were aerated. In others the lumens contained masses of fibrin and red cells. In other places there was an admixture of polymorphonuclear leukocytes. The bulk of the alveolar exudate appeared to be serous and mononuclear, particularly when numerous sections were examined. The fundamental and most uniform changes

consisted of round cell infiltration and edema involving pulmonary septums, peribronchial and bronchiolar tissues and alveolar walls, along with bronchiolar ulcerative changes. Microscopically, the hemorrhages in the brain were perivascular and showed no sign of organization. Many of them were large, covering about one half of a low power microscopic field. Regional blood vessels

the larger bronchial branches is in keeping with that of the upper respiratory tract. The scarcity of bacteria in lung tissue proper in inflamed areas is a finding not limited only to this case. Many others showed a similar scarcity (see foregoing comment on cases 1 to 13). Search for bacteria in several lung tissue sections of both lungs in this instance revealed a single staphylo-

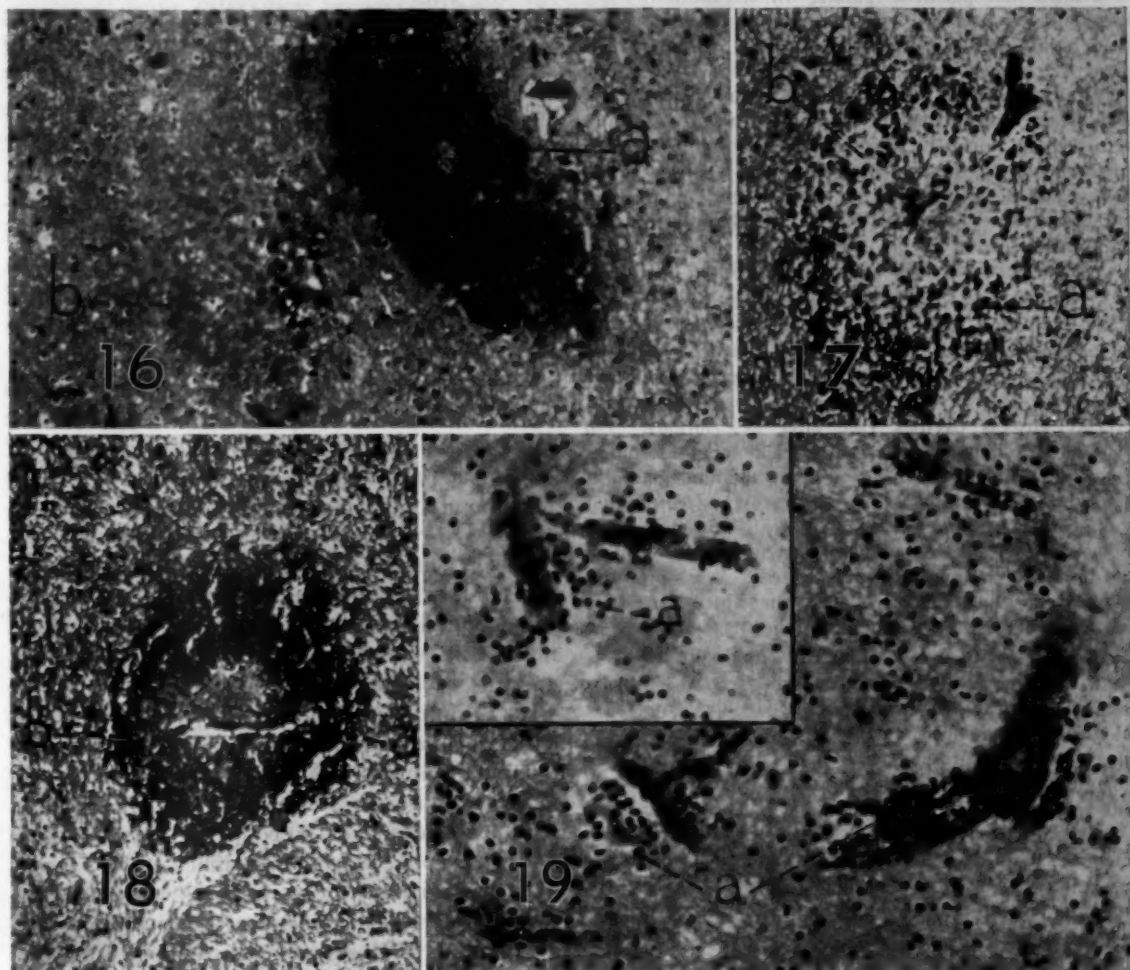


Fig. 16.—Negative 80513. Accession 86885.  $\times 120$ . In this section of cortex of the brain from a case of acute interstitial pneumonitis there are a patch of hemorrhage (a) and a focus of glial cell proliferation (b) in the white matter.

Fig. 17.—Negative 80517. Accession 86885.  $\times 120$ . Another focus in the brain of the same case as shown in figure 16, showing a glial cell collar (a) around a necrotic focus (b).

Fig. 18 (case 8).—Negative 80619. Accession 96956.  $\times 145$ . There is a necrotic center (a) in the midst of this hemorrhagic focus (b) in the brain in this case of acute interstitial pneumonitis.

Fig. 19.—Negatives 80684 and 80685. Accession 105744.  $\times 230$ . In this case there were seen small numbers of glia cells forming collars around blood vessels (a), as well as hemorrhagic encephalopathy (not shown in photograph).

showed glial collars. Nowhere could monocytic or lymphocytic exudates be identified perivascularly or otherwise. In the centers of some hemorrhagic areas small irregular foci of necrosis could be identified (fig. 18). There was no evidence of meningitis, nor could changes in ganglion cells be identified with certainty.

The relative absence of bacteria in postmortem cultures in this case is striking. The bacterial flora of

coccic cluster in one bronchiolar lumen and occasional gram-positive cocci in short chains and in pairs in a few other bronchioles. None were found in the thickened alveolar walls, in the inflamed peribronchial tissues or in the alveolar exudates. No organisms were demonstrable by tissue section in the foci of hemorrhage in the brain, or in the foci of glial proliferation.

CASE 12 (87961).—In this case acute interstitial pneumonitis was complicated by pulmonary abscess.

A white man 42 years old had an illness of nineteen days' duration which started with weakness, malaise and fever. There was substernal distress on coughing. The initial physical examination revealed only bilateral harsh breath sounds and coarse rhonchi. There was slight cyanosis of the lips. On the second day in the hospital the cough became more severe and productive of a thick mucopurulent sputum, which contained many hemolytic streptococci. Fever mounted to 104 F., and there was increasing cyanosis. The roentgenogram showed changes in the left lower lobe "typical of atypical pneumonia." Sulfadiazine therapy was started and by the seventh day in the hospital the temperature returned to normal. Two days later the pulse and respiratory rates became irregular, with signs of circulatory failure, which did not respond to digitalis and mercuraphylline injection U. S. P. The patient died on the nineteenth day in the hospital, with the fever going up to 106 F. and lapse into coma.

At autopsy the left lung weighed 720 Gm. and the right 1,140 Gm. The larger branches of the bronchial tree contained thick, green, frankly purulent material. The pleural surfaces were smooth except that of the lower lobe of the right lung, where fibrinous pleuritis overlay abscess cavities (see later description). On section both lungs showed peribronchiolar thickenings, the centers of which exuded pus. In addition, the right lung showed several abscesses of various size, ranging from a few millimeters to several centimeters in diameter. Direct communication with small bronchi and bronchioles could be demonstrated. Areas of frank lobular consolidation surrounded the abscess cavities but not the peribronchiolar thickenings.

On microscopic examination two pathologic processes could be demonstrated by appropriate section. Blocks from the left lung particularly showed only acute focal interstitial pneumonitis. Large areas of normal aerated lung tissue were present between the thickened bronchioles. On the opposite side there was a similar process plus extensive abscess formation. Where the two lesions approached each other, their microscopic characteristics tended to overlap, but by appropriate section one could demonstrate independent lesions. In the left lung the chief lesions were confined to the smaller bronchi and the bronchioles, which showed extensive mucosal ulceration and peribronchial interstitial round cell infiltration. On the right side, numerous abscess cavities were seen, some appearing to be a continuation of dilated inflamed bronchioles, while others showed extensive necrosis of alveolar walls.

Tissue sections from the region of the abscess cavities stained for bacteria showed many gram-positive cocci in short chains and in clusters on the mucosal surface of the larger bronchi and in the lumens of the smaller bronchi. The abscess cavities contained myriads of similar organisms, as did the zones of regional lobular consolidation. The portions of lung showing only acute interstitial pneumonitis showed occasional gram-positive cocci within bronchiolar lumens but none in the affected bronchiolar or alveolar walls or in any of the alveolar lumens.

The fact that one could separate two anatomic processes in this case is instructive. It appears reasonable to assume that the abscesses presented superimposed bacterial infection. This is borne out by the ease of the demonstration of bacterial forms in the abscess areas and the difficulty of finding any where there was only acute interstitial pneumonitis.

#### REVIEW OF THE LITERATURE

Volume 12 of the work entitled "Medical Department of the United States Army in the World War" reports pulmonary lesions in cases of influenzal pneumonia of the pandemic of 1918-1919. If one will select from that series those reports of cases in which death occurred in the first five days or so of illness, one will find described a group of anatomic lesions of the lungs like those described in the current series. When the clinical duration was greater than five to seven days in the influenza pandemic, secondary bacterial infection was the rule. Therefore, one finds in that volume descriptions of wet, dripping red lungs in geographic areas where streptococcal invasion was the rule and of bronchopneumonia and lobar pneumonia where pneumococcal invasion was common. A similar observation was made by MacCallum<sup>2</sup> in his studies of the same period, namely, that the fundamental anatomic lesion in some cases of influenzal pneumonia is one of acute interstitial pneumonitis. In fact, there is little that can be added in this report to the anatomic descriptions of acute interstitial pneumonitis made by that author. Furthermore, Shope,<sup>3</sup> reporting the spontaneous and experimental lesions of influenza in swine describes pure interstitial pneumonitis in experimental animals receiving the virus of influenza alone. McCordock and Muckenfuss<sup>4</sup> called attention to the tendency of viral pulmonary infections, particularly influenza and measles, to produce this type of pulmonary lesion. It appears reasonable to conclude, therefore, that influenzal pneumonia uncomplicated by secondary bacterial invaders produces lesions in the lung similar if not identical with those found in the "atypical pneumonia, etiology undetermined" of current interest. The observations of Scadding<sup>5</sup> add further confirmation of that assertion. In an account of a series of pathologically studied cases in England in which the virus was isolated, in small epidemics proved to be epidemics of influenza, he reports briefly on the pathologic changes in the lungs. The lesions reported are similar to the changes described in foregoing paragraphs. Generally, they are the lesions of acute interstitial pneumonitis.

2. MacCallum, W. G.: The Pathology of the Pneumonia in the United States Army Camps During the Winter of 1917-18, Monograph 10, Rockefeller Institute for Medical Research, 1919.

3. Shope, R. E.: Influenzas of Swine and Man, in Harvey Lectures, Baltimore, Williams & Wilkins Company, 1936, vol. 31, p. 183.

4. McCordock, H. A., and Muckenfuss, R. S.: Am. J. Path. 9:221, 1933.

5. Scadding, J. G.: Quart. J. Med. 6:425, 1937.

Of those published cases of "atypical pneumonia, etiology undetermined" in which study was completed by autopsy, 1 of 2 cases reported by Longcope<sup>6</sup> falls into the group in which the lesions were such as I have described. He observed in his first case with autopsy typical lesions of acute interstitial pneumonitis and reported foci of metaplasia to squamous cells in small bronchi. No bacteria were demonstrable in his tissue sections of the lungs. Mice and ferrets inoculated with ground lung material did not present signs of infection. Longcope's second case with autopsy in the same report was complicated by marked calcific aortic stenosis and chronic passive congestion of the lungs. That case showed advanced organization of a pneumonic process in which the acute interstitial component was masked to some extent at least. A similar complicating factor of pulmonary organization mars the pathologic interpretation of the process in the case observed by Kneeland and Smetana<sup>7</sup> (case 9), one of ten weeks' duration. Judging by the pathologic report of that case the lesion was one of chronic interstitial fibrosis of unknown cause. Certainly the long duration of illness in the case separates it markedly from the acute ones in my series. Dingle and co-workers<sup>8</sup> reported another case with autopsy in their excellent summary of the clinical, epidemiologic and roentgenologic observations on "primary atypical pneumonia." The lungs in their case showed acute interstitial pneumonitis with a pronounced hemorrhagic component. The same fundamental pulmonary lesion was noted in single autopsies reported by Needles and Gilbert<sup>9</sup> and by Lusk and Lewis,<sup>10</sup> respectively.

Cytoplasmic inclusion bodies in alveolar and bronchial epithelium were reported by Adams<sup>11</sup> in an epidemic of "primary virus pneumonia" in newborn infants. No such observations could be duplicated in my series of cases. Inasmuch as Adams' inclusion bodies were relatively large and stainable by hematoxylin and eosin, it is reasonable to assume that different diseases were encountered in his series and in mine.

McNaught<sup>12</sup> summarized briefly the autopsy observations in 6 cases of "virus pneumonia" from which there had been isolated a "psittacosis-like" agent. Inasmuch as no such agent had been isolated from any of my cases I must conclude again that the etiologic factor in his group of cases is different from that in mine. The fundamental pulmonary abnormality in McNaught's series appeared to have been fibrino-hemorrhagic exudate in pulmonary alveoli, which agrees fairly well with my observations on the pulmonary lesions in psittacosis.

A single case with autopsy was reported by Rothenberg.<sup>13</sup> In that case death occurred on the twenty-eighth day of illness and the illness was diagnosed clinically as "atypical pneumonia." Both clinically and pathologically the changes appear to this author to be consistent with an initial lesion of acute interstitial pneumonitis on which was superimposed lobular pneumonia.

Saphir<sup>14</sup> in discussing "atypical pneumonia" correctly defined the pathologic process as acute interstitial pneumonitis. In his report of an autopsy he stresses the diagnostic significance of the formation of a hyaline membrane in alveoli, the occurrence of which I have found to be a variable in my series.

Perrone and Wright<sup>15</sup> reported pulmonary lesions essentially like those I have described in their fatal case of "atypical pneumonia." The essential similarity is brought out particularly well in their photomicrographs. The autopsy showed hemorrhages in the brain, perivascular cuffs of "round cells" and "astrocytic and glial" proliferations. From a pathologic point of view the lesion of the brain which they observed and the ones described in my series deserve the name "hemorrhagic encephalopathy" rather than "encephalitis," at least until such time as pathologic-etiological correlations can be made.

There exists, therefore, a body of knowledge which bears out my fundamental thesis, namely, that the pathologic process of "atypical pneumonia, etiology undetermined" is acute interstitial pneumonitis. From my experience and that of others I can infer that similar lesions can be produced by at least a small number of infectious agents, including the poorly understood ones (see later comment on this) which are responsible for "primary atypical pneumonia." Lastly, it has been my observation

6. Longcope, W. T.: *Bull. Johns Hopkins Hosp.* **67**:268, 1940.

7. Kneeland, Y., Jr., and Smetana, H. F.: *Bull. Johns Hopkins Hosp.* **67**:229, 1940.

8. Dingle, J. H.; Abernethy, T. J.; Badger, G. F.; Buddingh, G. J.; Feller, A. E.; Langmuir, A. D.; Rueggesser, J. M., and Wood, W. B., Jr.: *Am. J. Hyg.* **39**:67, 1944.

9. Needles, R. J., and Gilbert, P. D.: *Arch. Int. Med.* **73**:113, 1944.

10. Lusk, F. B., and Lewis, E. K.: *Dis. of Chest* **10**:19, 1944.

11. Adams, J. M.: *J. A. M. A.* **116**:925, 1941.

12. McNaught, J. B.: *California & West. Med.* **59**:220, 1943.

13. Rothenberg, R. C.: *Cincinnati M. J.* **24**:152, 1943.

14. Saphir, O.: *Radiology* **40**:339, 1943.

15. Perrone, H., and Wright, M.: *Brit. M. J.* **2**:63, 1943.

and that of others that the soil prepared by an infection which results in acute interstitial pneumonitis is prone to secondary bacterial infection. When that occurs, one finds superimposed hemorrhagic pneumonia, lobular or lobar consolidations or pulmonary abscesses, depending on the properties of the invading pathogens.

#### COMMENT

There were variations in the morbid anatomy in this series of cases of acute interstitial pneumonitis, as will be noted from the general pathologic description of the pulmonary lesions and from the report of specific cases in this article. The pathologic changes which all cases had in common can be summarized as follows:

1. There was acute bronchiolitis, focally distributed, in which desquamation of the mucosal surfaces occurred early.

2. The lumens of such bronchioles contained frank pus, mucoid fluid and desquamated epithelial clusters or single cells, sometimes in an advanced stage of disintegration.

3. Bacteria in small numbers and not of uniform type could be demonstrated in the bronchiolar pus in some cases; in most cases none could be found.

4. The bronchioles were dilated, sometimes markedly, even in cases in which death occurred early in the disease.

5. The walls of such bronchioles were infiltrated chiefly with mononuclear cells, which extended radially into the regional interstitial tissues of the lung, namely, the peribronchiolar tissues, the alveolar walls and the pulmonary septums.

6. The alveoli either contained air or were collapsed, and differed from those involved in bronchopneumonia and lobar pneumonia in being relatively free of polymorphonuclear leukocytic exudate.

7. Such areas failed to reveal micro-organisms on tissue section.

8. With the advent of secondary bacterial invasion, the gross and microscopic pictures were altered: In some cases it was possible at autopsy to discover areas of acute interstitial pneumonitis adjacent to zones of typical bronchopneumonia, lobar pneumonia or pulmonary abscess. In fact, unless there was such a partition of the lesions, it was impossible to state from the pathologic examination that there were really two co-existing lesions in a given case.

The presumption is strong that one or more nonbacterial agents cause this type of acute interstitial pneumonitis. The chief evidence from

this pathologic study is found in the inability to demonstrate consistently any organisms in the lung tissue other than those in bronchiolar lumens. Such bronchiolar organisms are probably derived from the normal respiratory flora, although it cannot be denied that they may play some role in the infection. This apparent freedom from bacteria in tissues where round cell exudation is seen contrasts markedly with the ease of the demonstration of microbial forms as soon as bronchopneumonia, lobar pneumonia or abscess formation appears.

Further evidence of the viral nature of this infection is found in the similarity of the lesion to that seen in some cases of acute influenzal pneumonia, particularly in those in which death occurs in about the first five days of illness. Presumably, the patients succumb to the virus infection before secondary bacterial infection sets in. In measles one may see similar pneumonitis. However, a bacterial infection, such as pertussis, is capable of producing acute interstitial pneumonitis too, in which case *Haemophilus pertussis* can be demonstrated in tissue sections.

This speculative dissertation will remain just that until the cause of this infection is demonstrated beyond question. In Francis' <sup>16</sup> summary of the work done to date along the lines of etiologic research, it is clear that several promising avenues of investigation have been opened, in none of which the workers can claim universal acceptance of their findings. Therefore, I shall leave to the future the question whether the variations in lesions seen in the lungs and described in the foregoing pages, such as alveolar membranes, edema and hemorrhage, represent individual differences or specific lesions in response to specific agents.

The acute dilatation of affected bronchioles is observed fairly constantly. One would expect that complications might ensue, such as chronic bronchiectasis. To date no cases in which this occurred have come to my attention pathologically. On the other hand, actual necrosis of bronchial walls was seen but once. In the remainder of the cases the lesions were of two types. In lesions of one type the bronchial walls were merely edematous, congested and heavily infiltrated with round cells. It is perfectly consistent with the known processes of repair that such lesions could resolve without leaving any appreciable damage. In lesions of the other type, frequently seen in the same case, one could demonstrate in small bronchi and bronchioles marked dilatation, destruction of the

16. Francis, T., Jr.: *Canad. Pub. Health J.* **35**:49, 1944.

elastic fibers, fragmentation of the muscle bundles and shredding of the reticular meshwork. Such lesions probably could heal only by persistent dilatation and scar formation. This is not meant to imply that all such lesions could or would ever become clinically manifest as chronic bronchiectasis.

It is not clear why the lumens of small bronchi and bronchioles should contain quantities of polymorphonuclear leukocytes while the surrounding tissues show predominantly round cell exudation. One might postulate that the primary cell attacked is that of the bronchiolar mucosa, which undergoes necrosis and desquamation, leaving an ulcerated surface. The polymorphonuclear response could be, therefore, a response to the denudation of a surface. If a virus is in fact the cause of this disease, the round cell interstitial exudate would be in keeping with the known leukocytic responses to viruses in general.

In the few cases in which lesions of the brain were found, they were of the hemorrhagic type. Pathologically, the encephalic process deserves the designation hemorrhagic encephalopathy (figs. 16 to 19), and except for their frequently inordinately large size the lesions are entirely compatible with those seen in anoxic states. However, some of the lesions in this series show not only hemorrhages but perivascular cuffs of glia cells near the hemorrhages and small zones of necrosis in the centers of the hemorrhages. Therefore, a direct injurious effect of the etiologic agent cannot be ruled out. As for the hyaline necrosis of diaphragmatic muscle fibers, the lesion is nonspecific in the sense that it is seen in various infections, notably typhoid, influenzal pneumonia and other septic states induced by micro-organisms. Its consequences may be serious from the point of view of the welfare of the patient. It is entirely conceivable that when the lesion is widespread the interference with the normal movements of the diaphragm could add to the respiratory distress so characteristic of the clinical state. The relatively benign changes in the regional lymph nodes are consistent with nonbacterial pneumonia.

The examinations of sputum in this series revealed variable bacteriologic and gross features. Routine bacteriologic examinations during life failed to reveal a uniform bacterial flora and many times only a very scanty bacterial flora of any kind. Typable pneumococci were found only rarely. Grossly there was much variation in the composition of the sputum. In the early stages of the infection little or no sputum could be raised. Later small amounts of mucoid sputum and mucopurulent or seromucoid speci-

mens were the rule. In only a small number of cases was blood seen in the sputum. It should be emphasized that these are the characteristics of patients so severely ill as to succumb to the infection.

The leukocyte count in this series tended to be high. Sample counts from 5 cases are given in table 2. In general, the leukocytosis showed a polymorphonuclear predominance, ranging in cases cited in table 2 from 70 to 98 per cent. This is not in entire agreement with the figures of Meyer and Thewlis,<sup>17</sup> who reported normal numbers of white blood corpuscles per cubic millimeter, with increases in the percentages of polymorphonuclear leukocytes in the earliest stages of the infection and stated that with clinical improvement the total white blood cell count rose, with a return of the differential count to normal. Again it should be emphasized that this series is one of cases which came to autopsy. It may be that the tendency toward leukocytosis

TABLE 2.—Leukocyte Counts in Five Cases

Accession No.	White Blood Cells per Cu. Mm.	
	Initial	Peak
86885.....	8,000	22,500
111304.....	22,000	.....
97140 (case 6).....	6,000	11,950
79891 (case 3).....	17,000	58,700
71380 (case 4).....	8,000	32,000

is a manifestation of the severity of the infection and is perhaps of serious prognostic significance.

The test for cold agglutinin was performed in only a small number of these cases and the agglutinin was of significantly high titer (for example, 1:1,024 in accession 99535). From the small number of cases examined no conclusions can be drawn in this report as to the correlation between that serologic test and the morbid anatomic picture.

In a discussion of the genesis of cyanosis in this disease, Saphir<sup>14</sup> postulated that the hyaline membranes lining alveoli are the chief barrier to proper gaseous interchange. I cannot accept that premise unreservedly inasmuch as the formation of hyaline membranes in the lungs was a variable in my series while cyanosis was common, if not universal. There are several other lesions which in my opinion deserve consideration with reference to the genesis of the cyanotic state in this disease. They are the massive plugging of the smaller branches of the bronchial tree by pus, the interstitial round cell infiltration of alveolar walls immediately surrounding the

17. Meyer, O. O., and Thewlis, E. W.: Proc. Central Soc. Clin. Research **16**:40, 1943.

capillary bed of the lung and the universal congestive picture seen in the lung. To these changes may be added the variable lesions of alveolar lumens which are expressed not only in the formation of hyaline membranes but also in the formation of the serous and fibrinous exudation, and hemorrhage.

#### SUMMARY AND CONCLUSIONS

The anatomic lesions of acute interstitial pneumonitis were studied in a large number of cases of death from "atypical pneumonia, etiology undetermined." The chief lesions of the lungs were seen to be comparable to those of certain other infections, notably of influenzal pneumonia uncomplicated by secondary bacterial infection and of uncomplicated measles pneumonia. There is anatomic evidence indicating but by no means proving that these lesions are caused by one or more viruses. It has further been brought out that some persons dying of the disease succumbed to both acute interstitial pneumonitis and the effects of secondary pulmonic bacterial infection,

such as lobular or lobar pneumonia. The exact interpretation of all the variations of the pulmonary lesions and of the lesions of the brain must await etiologic-pathologic correlations.

A review of the literature has shown the essential similarity of the lesions of the lungs in the acute interstitial pneumonia observed in my group of cases to those seen in animals and man in epidemic influenza and in measles. Other investigators who have studied isolated cases of death from this disease in the last ten years (see foregoing review) have reported changes in the lungs and the brain essentially like those described by me.

The illustrative cases presented bring out the anatomic unity of this pulmonary lesion. The features of the lesion are not new, since similar lesions have been described in other diseases. This must not be taken to mean, however, that the clinical disease or the etiologic agents have been seen clinically or epidemiologically in the past. Entirely different lines of investigation are required to solve that point.

## AMYLOIDOSIS IN ATYPICAL SITES (CARDIAC VALVES, LARYNX)

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There are 24 reported cases of primary systemic amyloidosis. In all except 1 of these cases the heart was involved in varying degrees and in only 2 of those cases was amyloid present in the tricuspid and mitral valves. In the case reported by Wild,<sup>1</sup> in addition to amyloidosis of the valves, there were deposits in the tongue, the heart, the pericardium, the gastrointestinal tract, the lymph nodes, the bladder, the lungs and the peritoneum. The other case was that of Koletsky and Stecher,<sup>2</sup> who reported involvement of the tongue, the heart, the skeletal muscles, the intestines, the joints, the bones, the tendons, the vagina and the lips, as well as deposits in each of the cardiac valves. In the rare cases of primary isolated amyloidosis of the heart the valvular involvement is also usually insignificant with the exception of the case reported by Koller,<sup>3</sup> in which the mitral and tricuspid valves were extensively involved.

In secondary amyloidosis, amyloid deposits are rarely present in the valves and usually only in insignificant amounts. However, here again there is an exception in Israel's<sup>4</sup> case, in which the amyloidosis may have been secondary to cirrhosis of the liver and in which there were extensive deposits in both the mitral and the tricuspid valve.

Jaffé<sup>5</sup> noted that in experimental production of amyloid in mice by rapid injection of sodium caseinate, amyloidosis of the heart occurred; the amyloid was not only deposited about the vessels of the myocardium but was also present in the valve leaflets, particularly in those of the mitral valve.

A case will now be reported in which, in addition to marked deposits of amyloid in the tricuspid and mitral valves, there was extensive amyloidosis of both auricular walls, of the epi-

cardium and the myocardium, of the larynx and vocal cords and around the venules and arterioles in the periadrenal fat.

### REPORT OF A CASE

A 61 year old white man had three admissions to the first medical division of Bellevue Hospital. He was first admitted Oct. 12, 1943 with a complaint of hoarseness and cough of one year's duration. He had had a chronic nonproductive cough for many years but was generally well until one year before admission, when he noted hoarseness, loss of appetite and cough productive of a half cupful of sputum a day. He had lost 43 pounds (19.5 Kg.) during this year though there was no history of a poor intake of food. He had noted occasional substernal pain and increasing dyspnea for three months immediately prior to admission.

On admission the temperature was 100 F., the pulse rate was 96 and the blood pressure was 140 systolic and 70 diastolic. The patient was poorly nourished, dyspneic and cyanotic but not orthopneic. He was able to talk only in a hoarse whisper. The head, including the ears, the nose and the throat, showed no abnormalities with the exception that on direct laryngoscopy the left vocal cord revealed immobility. The veins of the neck were distended; the heart seemed to be enlarged to the left; the sinus rhythm was regular, and the aortic second sound was greater than the pulmonic second sound. An occasional extrasystole was present. No murmurs were noted. Many rhonchi and rales were heard over the lower part of the chest both anteriorly and posteriorly. The liver and the spleen were not palpable, and no abdominal masses were felt. The fingers were slightly clubbed, and there was moderate edema of the lower extremities. Rectal examination disclosed nothing unusual. All reflexes were normal. There was no enlargement of lymph nodes. No abnormalities of the skeletal system were noted.

The hemoglobin content was 14 Gm. (Sahli method); the red blood cell count was 4,150,000; the white blood cell count was 14,850; the differential count was polymorphonuclear leukocytes 83 per cent, lymphocytes 16 per cent and mononuclears 1 per cent. The specific gravity of the urine was 1.006 to 1.018; albumin (2 plus) was present in six specimens. On one occasion a few hyaline casts were seen. Culture of the sputum showed the presence of staphylococci, gram-negative bacilli, nontypable pneumococci and Streptococcus viridans. Culture of blood gave no growth. The erythrocyte sedimentation rate was 39. The Wassermann test was negative. The blood nonprotein nitrogen was 30 mg., the serum albumin 3.2 Gm. and the serum globulin 1.8 Gm. per hundred cubic centimeters. The electrocardiogram revealed left axis deviation with a low QRS complex in all leads. A roentgenogram of the chest taken Oct. 13, 1943 revealed irregular, mottled areas of density in the lower half of the left lung. A roentgenogram of the chest taken October 22 showed thickened pleura of the lower

From the Laboratories of Pathology, Bellevue Hospital.

1. Wild, C.: Beitr. z. path. Anat. u. z. allg. Path. **1**:177, 1886.

2. Koletsky, S., and Stecher, R. M.: Arch. Path. **27**:267, 1939.

3. Koller, F.: Schweiz. med. Wchnschr. **13**:522, 1932.

4. Israel, I.: Ein Fall von lokalen Amyloid, Med. Dissert., Tübingen, Bochum-Langendreer, 1933.

5. Jaffé, R. H.: Arch. Path. **1**:25, 1926.

part of the chest on the left, as a result of which it was impossible to exclude underlying pneumonic consolidation. While in the hospital the patient had a temperature of 100 to 101 F. for twelve days. A six day course of treatment with sulfadiazine did not appear to affect the progress of the disease. From the thirteenth to the fortieth day of this stay in the hospital the patient was afebrile but again had a low grade fever for about seven days. He was afebrile for the last ten days in the hospital.

On the tenth hospital day a pleural effusion was noted on the left, and 750 cc. of clear yellow fluid was withdrawn. The specific gravity of this fluid was 1.012, and it contained 170 red blood cells and 326 white blood cells, 24 per cent of which were polymorphonuclear leukocytes, 68 per cent lymphocytes and 8 per cent mesothelial cells. Culture of the fluid produced no evidence of infection. Another thoracentesis on the fifteenth day again yielded 750 cc. of fluid with 620 white blood cells, 41 per cent of which were polymorphonuclear leukocytes, 45 per cent lymphocytes and 14 per cent mesothelial cells. Again culture of the fluid yielded no growth. The venous pressure at this time was 42. The circulation time for dehydrocholic acid was thirty-five seconds; that for ether, seventeen seconds.

Direct bronchoscopy revealed the left vocal cord immobile, as stated. Bronchoscopy showed the right bronchus to be normal while the mucosa of the left main bronchus was hyperemic and ulcerated just above the bifurcation. There was much secretion coming from the right bronchus. Bronchoscopy somewhat later in the chest division of the hospital disclosed nothing of significance; no ulcer was seen at this time. The patient gradually improved and was discharged for convalescent care.

He was again admitted to the hospital Jan. 26, 1944 because of constant cough productive of copious greenish yellow sputum that was never foul or bloody. The loss of weight and the hoarseness had both increased. There was increasing weakness. He appeared chronically ill but in no acute distress. At this time there were bilateral rhonchi, wheezes and numerous rales throughout both lungs except at the extreme apices. The cardiac findings were unchanged and no edema was noted.

The hemoglobin content was 13.9 Gm. (Sahli); the red blood cell count was 4,200,000, and the white blood cell count was 10,250, 82 per cent of which were polymorphonuclear leukocytes, 16 per cent lymphocytes, 1 per cent eosinophils and 1 per cent mononuclears. Examination of the urine and the sputum gave essentially the same results as after the previous admission. Examinations of the stools revealed no blood and no parasites. The erythrocyte sedimentation rate was 61. The bleeding time was one and one-half minutes; the clotting time, one minute. The platelet count was 270,000. The patient was in the hospital for thirty-eight days. During this time he was afebrile. Direct laryngoscopy at this time revealed paralysis of both vocal cords. Nothing abnormal was discovered on bronchoscopic examination. The renal and gastrointestinal tracts were investigated roentgenologically, but nothing of significance was observed. The pulmonary symptoms continued unabated. The patient then left the hospital.

He was admitted again May 4 with essentially the same complaint of productive cough. In addition there were marked dyspnea, orthopnea and extreme weakness. The cough now seemed almost paroxysmal, and he was intensely cyanotic. The temperature was 106 F., the pulse rate 92, the respiratory rate 40, and the blood pressure 130 systolic and 80 diastolic. There were no

new findings since the previous admission. The hemoglobin content was 12 Gm.; the white blood cell count was 8,650, 81 per cent of which were polymorphonuclear leukocytes and 19 per cent lymphocytes. The Wassermann reaction of the blood was negative. Examination of the sputum showed type IX pneumococci with occasional hemolytic streptococci. Examination of the urine showed a specific gravity of 1.020 and albumin (2 plus).

The patient was examined by fluoroscope on admission, and in addition to what appeared to be diffuse fibrosis and obliteration of the right costophrenic angle, there was a mottled infiltration of the right lung field. Sulfadiazine therapy was started. The patient became extremely restless, pulling out the intranasal catheter by which oxygen was being administered, and died twelve hours after admission.

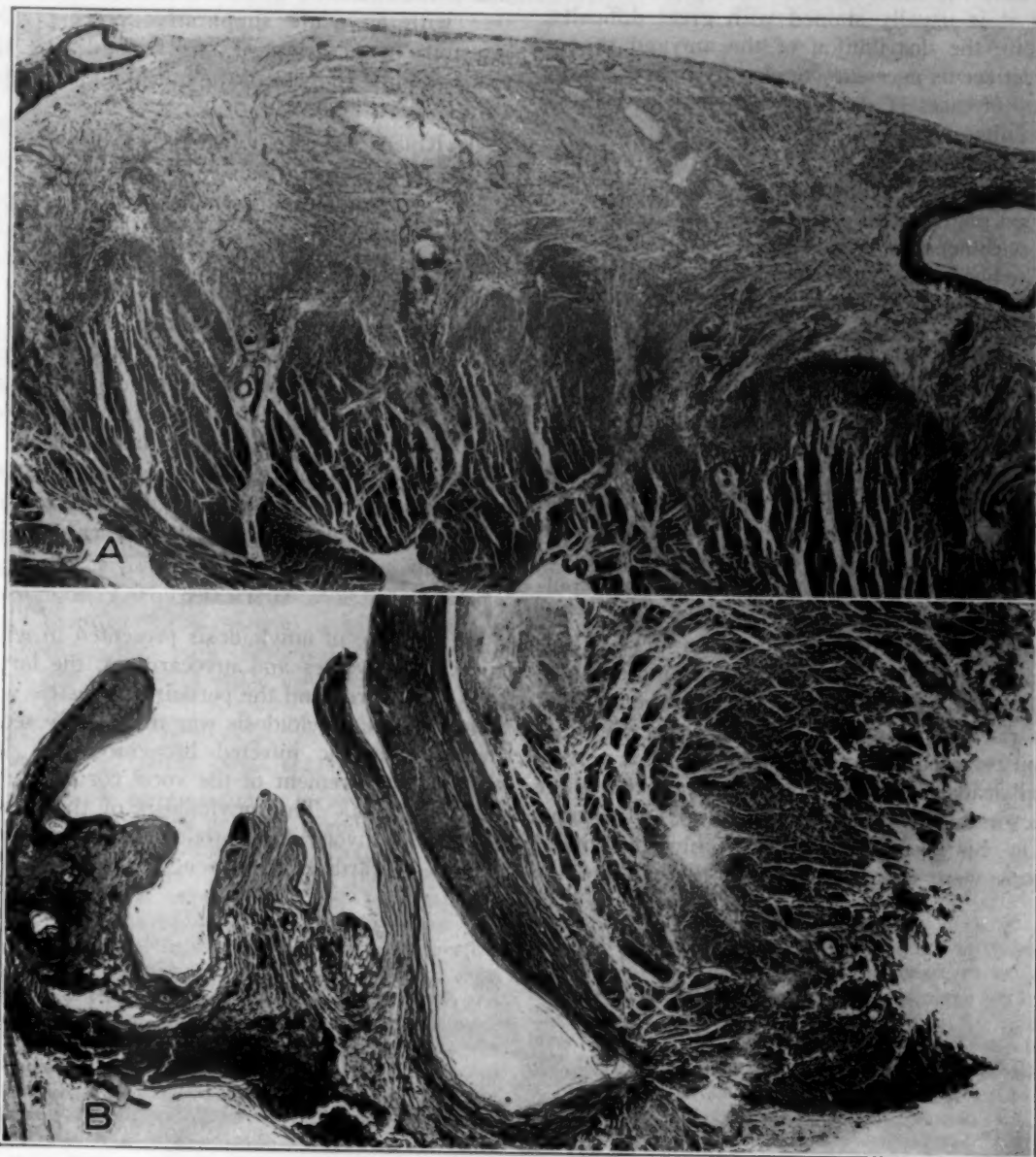
*Postmortem Examination* (five days after death).—The body was that of a fairly well developed and well nourished white man. Aside from slight clubbing of the fingers there were no external abnormalities of any significance. The pericardial sac contained 125 cc. of clear yellow fluid. The pericardium was smooth and glistening. The heart weighed 460 Gm. The myocardium was pale brown and without areas of fibrosis. The endocardium was smooth, waxy and yellow. The left and right auricular chambers were enlarged and had thickened, rigid, leathery walls, in which there was an abundance of firm yellowish white material. Both ventricles were of normal size. The right ventricular wall measured 3.5 mm. and the left 15 mm. The coronary arteries were normal. The pulmonary and aortic valves appeared delicate and patent. The mitral and tricuspid valves were thickened, rigid, waxy and yellow. The chordae tendineae of these valves were only slightly thickened and not fused together or shortened. The aorta had moderate atherosclerotic change.

Numerous bilateral fibrous pleural adhesions were present. The right pleural cavity contained 100 cc. of straw-colored fluid. The lungs were subcrepitant throughout and on section revealed a diffuse dilatation of all the bronchi and bronchioles with thick whitish purulent material in the lumens. There were occasional diffuse patches of gray consolidation scattered throughout. The tracheobronchial lymph nodes were firm, small and black. The liver weighed 1,600 Gm. and on section revealed congestion and accentuation of the lobular architecture. The spleen weighed 200 Gm. and was firm; the capsule was thickened. On section the malpighian corpuscles and trabeculations were prominent. The pancreas, the adrenal glands, the kidneys, the bladder, the prostate, the testes, the gastrointestinal tract and the bone marrow were not unusual. Both vocal cords were thickened and infiltrated with a yellowish white material. This material extended for a considerable distance from the vocal cords, involving the entire larynx. The other organs of the neck were normal. The brain was not examined. The larynx, the myocardium and the cardiac valves were stained with iodine and hydrochloric acid, and the yellowish white material was colored mahogany brown.

*Histologic Examination.*—Sections were made and stained with hematoxylin-eosin, crystal violet and congo red. Sections through the ventricles of the heart revealed mild hypertrophy of the muscle fibers. In the small coronary vessels, especially the arteries, there was subendothelial and medial deposition of an eosin-stained homogeneous material that gave a reaction with congo red and crystal violet for amyloid. The myocardial fibers were occasionally interrupted by nodular deposits of the same substance, particularly of the subendocardial

and epicardial regions (*A* in the figure). The involvement of both the left and the right auricle was extensive, with almost complete replacement of the muscle by this amyloid. The mitral ring and valve contained similar extensive nodular deposits of amyloid (*B* in the figure). This was also true of the tricuspid ring and

*Anatomic Diagnosis.*—The following conditions were diagnosed: diffuse cylindric infected bronchiectasis; amyloidosis of the myocardium and the tricuspid and mitral valves, of the larynx and vocal cords and of the periadrenal venules and arterioles; chronic passive congestion of the liver and the spleen; lobular pneumonia.



*A*, microscopic section through the myocardium and the epicardium showing amyloid involvement. Hematoxylin-eosin;  $\times 12$ . *B*, microscopic section through the mitral valve showing amyloid involvement of both the ring and the cusp. Hematoxylin-eosin;  $\times 12$ .

valve. The lungs revealed infected cylindric bronchiectasis and areas of edema with lobular pneumonia. There was no evidence of any deposition of amyloid. In the liver and the spleen there was moderate passive hyperemia; no amyloid was found. The adrenal glands were autolyzed; there were amyloid deposits in the venules and arterioles of the periadrenal fat. The kidneys and the pancreas were normal. There were extensive deposits of amyloid in the larynx and vocal cords.

#### COMMENT

The distribution of the amyloid in this case was typical of that usually observed in primary systemic amyloidosis, but in this uncommon form of amyloidosis no chronic underlying infection was present and the amyloid was deposited in such atypical sites as the tongue, the larynx, the

skin, the skeletal and smooth muscles, the heart, the intestinal tract, the joints, the tendons and the urinary bladder. The usual sites, such as the spleen, the liver and the kidneys, were not involved. Often in this form the amyloid does not take the usual specific stains, and when it does it is usually stained with great difficulty. Despite the distribution of the amyloid in our case, it seems necessary to classify it in the large group of cases of secondary amyloidosis because a definite underlying chronic suppurative infection was present in the form of diffuse cylindric bronchiectasis. Furthermore, the amyloid stained readily with iodine and hydrochloric acid and with congo red and crystal violet.

The hoarseness that was erroneously attributed to paralysis of the vocal cords was most likely due to the extensive amyloid deposits. If this is true, the amyloid must have been present for at least two and one-half years, as the hoarseness had been present for that period.

To what extent the involvement of the myocardium and cardiac valves produced clinical manifestations is not clear. On the first admission, the veins of the neck were distended, and the patient was dyspneic and cyanotic. There was also edema of the legs. However, a pulmonary infection was present at this time. But following the apparent regression of the pulmonary infection, a pleural effusion developed and the circulation time was increased without any rise in venous pressure. An electrocardiogram revealed left axis deviation and low voltage in all leads. It is possible, therefore, that there was some evidence of cardiac failure at this time.

On his second admission only pulmonary lesions were discoverable. At the time of the

final admission, when the patient was in the hospital just one day, there were marked cyanosis, dyspnea and orthopnea. Again much of this symptom complex can be at least partially explained on the basis of respiratory insufficiency due to the extensive involvement of the bronchial tree with an acute suppurative process. No murmurs were heard at any time despite the extensive involvement of the mitral and tricuspid valves.

In Koletsky's case extensive involvement of the aortic and mitral valves resulted not only in the production of murmurs but in hypertrophy of the left and right ventricles. There was also evidence of marked chronic passive congestion of the liver and the spleen in his case.

In those cases without deposits of amyloid in the valves it is thought that the circulatory changes are dependent on amyloid deposits reducing the lumens of the smaller coronary vessels, thereby producing an insufficiency of coronary circulation. It is not believed that the amyloid deposits in the myocardium itself are sufficiently extensive to result in cardiac impairment.

#### SUMMARY

In the case of amyloidosis presented in which the cardiac valves and myocardium, the larynx and vocal cords and the periadrenal vessels were involved, the amyloidosis was most likely secondary to chronic infected bronchiectasis. The amyloid involvement of the vocal cords resulted in hoarseness. The amyloidosis of the cardiac valves and myocardium produced only a minimal degree of cardiac insufficiency.

## LEIOMYOMA OF THE STOMACH

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The high incidence of leiomyoma of the stomach has seldom been noted. While this smooth muscle tumor has been generally recognized as the most frequent type of noncancerous gastric neoplasm, there are still many reports which refer to it as being rare. In 1938 Collins and Collins<sup>1</sup> found reports of 539 cases in the literature and estimated them to make up about 40 per cent of all cases of noncancerous gastric neoplasm. However, the majority of cases of leiomyoma of the stomach that have been reported are those in which it was treated surgically, while cases without signs or symptoms have usually gone unreported.

During the course of more detailed gross and microscopic examination of stomachs at autopsies, due to increased interest in gastric disease in general, I frequently encountered small incidental tumors which were diagnosed as leiomyoma. Because of the remarkably high incidence and because this high incidence is not appreciated, an analysis of these cases of leiomyoma seems of interest.

### MATERIAL AND METHOD

To determine more accurately the true incidence of leiomyoma, the stomachs from 50 autopsies were studied carefully both grossly and microscopically for the presence of tumors of this type. The cases for the series were chosen at random, except that cases in which the stomach was involved in adhesions or in primary or secondary cancer were discarded. The most important technic of the examination was careful palpation, since many of the tumors with this diagnosis were small and difficult to find by inspection alone. After removing the serosal fat, the stomachs were opened along the greater curvature. They were then spread, mucosal surface down, on a smooth dissecting board to facilitate the palpation of the entire gastric wall. By this method of examination it was possible to find one or more tumors of this type in 23 of the 50 stomachs. Forty-four tumors of this type were found (table 1).

The number found in the individual stomach varied from one to six, 11 stomachs having more than one and 2 having six.

This investigation was aided in part by a grant from the Anna Fuller Fund.

From the Laboratories of Pathology of the New England Deaconess Hospital, and the Pondville Hospital, Massachusetts Department of Public Health.

1. Collins, F. K., and Collins, D. C.: *West. J. Surg.* 46:188, 1938.

The tumors were somewhat more common on the anterior wall and were most frequent in the fundus, especially near the cardia (table 2).

The size of the tumors varied up to 0.7 cm. in greatest diameter. The commonest size was between 0.4 and 0.6 cm. in diameter. While the tumors were often difficult to note from the mucosal surface, they were usually visible from the serosal surface. None was pedunculated or ulcerated. One stomach had in addition a lipoma, 2 showed gastric polyps, and 1 had a microscopic focus of metastatic carcinoma in the gastric mucosa.

The ages of the patients in the entire series of 50 cases varied from 19 to 82 years, the majority being over 50 years. Those whose stomachs showed leiomyoma varied from 30 to 78 years, and the majority were likewise over 50 years. Ten of the 21 women and 13 of the 29 men showed tumors of this type.

TABLE 1.—Incidence of Gastric Leiomyoma

Number of stomachs examined.....	50
Stomachs with leiomyoma in one or more sites.....	23
Stomachs with multiple leiomyoma.....	11
Total number of cases of leiomyoma.....	44

TABLE 2.—Location of Leiomyoma in the Stomach

	Tumors
Anterior wall.....	26
Posterior wall.....	18
Fundus.....	39
Body.....	4
Antrum.....	1

Microscopically, all the tumors arose in and from the muscularis of the gastric wall; none appeared to arise from the vascular walls or from the muscularis mucosae. They were usually found in the outer or the middle layer of the muscularis. Most were ovoid, the long axis being parallel to the gastric wall. The majority were well defined or encapsulated; those that were ill defined showed no evidence of an invasive nature. The adjacent structures were usually compressed, and the overlying mucosa was often thinned (*A* in the figure).

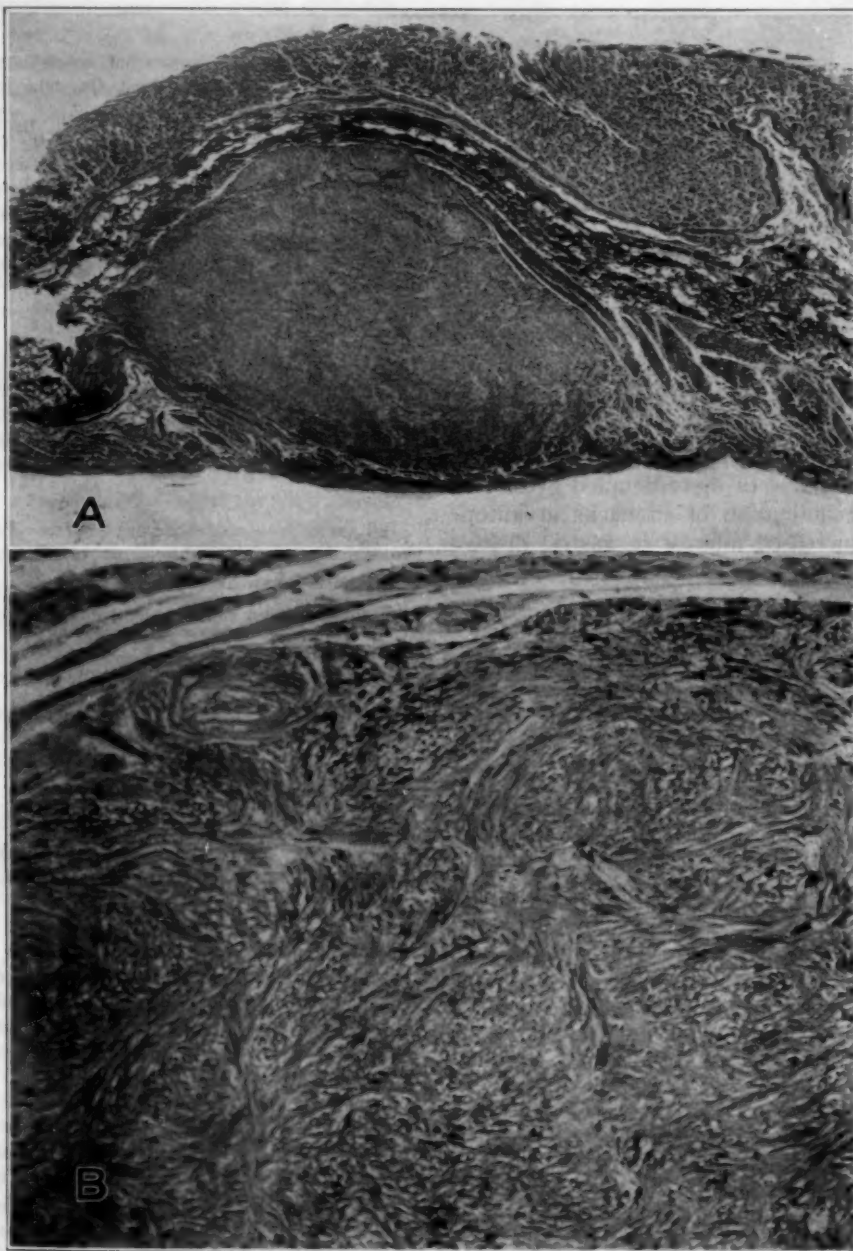
The tumors were composed of interlacing bundles of spindle-shaped smooth muscle cells (*B* in the figure). These muscle bundles when compared with the normal smooth muscle bundles of the adjacent gastric wall were shorter and had a more tangled relationship and pattern. The cells tended to clump together into a more compact arrangement than the normal, giving the impression of foci of increased cellularity. The individual cells were well differentiated and were uniform in size and shape. When stained with Masson's trichrome or Van Gieson's stain, the cells showed the characteristic appearance of smooth muscle. The nuclei were cigar shaped and

were slightly more pleomorphic and hyperchromatic than the nuclei of normal smooth muscle. There were no multinucleated cells and no tumor giant cells. All these tumors seemed relatively inert microscopically; in most no mitoses could be found. Even those that showed the most cellularity and disorientation contained only rare mitotic figures.

tumors showed central deposition of calcium of varying degrees.

#### COMMENT

The high incidence (46 per cent) of leiomyoma in this series of 50 stomachs suggests that gastric



Leiomyoma of stomach: A,  $\times 23$ . B,  $\times 160$ .

While there was often considerable adult collagen present, this appeared to be only supporting stroma of the cell bundles and not an active part of the tumors. Blood vessels were not prominent in the lesions.

Degenerative changes were common, the most frequent being fibrosis and hyalinization, chiefly central; in some, this was outstanding. At times there was scattered infiltration by lymphocytes. Four of the

tumors of this type are not rare but are among the commonest tumors of the body. It is comparable to the incidence of leiomyoma of the uterus, estimated by Klob<sup>2</sup> to be 50 per cent in

2. Klob, in Ewing, J.: *Neoplastic Diseases*, Philadelphia, W. B. Saunders Company, 1940, p. 233.

women over 50 years. In 200 consecutive autopsies at the Mayo Clinic, Rieniets,<sup>3</sup> in 1930, reported 32 as demonstrating one or more small gastric tumors diagnosed as leiomyoma which were similar in distribution and in gross and microscopic appearance to the tumors described in this paper. The other incidental tumors of the stomach diagnosed as leiomyoma in the laboratory with which I am associated were also similar in all respects.

The likeness of gastric to uterine leiomyoma is immediately apparent histologically. Not only is the structure identical, but the same collagenous stroma, the frequent hyaline changes and even calcification are present. While there was at times palisading of the nuclei, this fact alone should not cause confusion with neurilemmoma.

Why leiomyoma of the stomach should be so frequent is unknown. The frequent occurrence near the cardia is curious but sheds no light on the causes. There was an insufficient number of the tumors in the lower age groups to determine how many might have been originally anomalies of the musculature. Borrmann<sup>4</sup> expressed the belief that they almost certainly arise from displaced embryonic cells and that the fact that they are more often seen in older people may be due to their very slow growth. There was no apparent difference in incidence between males and females. I have only once observed a tumor of this type to be adjacent to a peptic ulcer, and here it seemed entirely incidental.

Ten specimens of leiomyoma and 11 of leiomyosarcoma of the stomach removed surgically are in the files of this laboratory, in comparison

with the nearly 700 stomachs resected for carcinoma. Aside from the larger size and the frequent mucosal ulceration the surgically removed specimens were indistinguishable from the smaller tumors noted incidentally at autopsy. It is interesting that such a small percentage of these tumors grow large enough to develop clinical significance. Those that do enlarge often cause progressive thinning of the overlying mucosa until the characteristic ulceration and hemorrhage<sup>5</sup> occur. Thinning of the overlying mucosa was noted even with many of the small tumors. When those in the antrum enlarge they may cause obstruction.

Since all gradations seem apparent between the noncancerous and the cancerous smooth muscle tumors, it is quite possible that in some cases leiomyosarcoma may arise from leiomyoma. In 1 case of leiomyosarcoma leiomyoma was present as two small tumors in the muscularis immediately adjacent to the main lesion.

#### SUMMARY AND CONCLUSIONS

Leiomyoma of the stomach is a common type of tumor. It was observed in 46 per cent of a series of 50 routine autopsies on adults. It may be multiple. The tumors arise from the muscularis of any portion of the stomach but are most frequent in the fundus, especially near the cardia.

Leiomyoma of the stomach occurs with about equal incidence in males and females. It is histologically indistinguishable from leiomyoma of the uterus and shows similar hyaline changes and calcification.

While common, gastric leiomyoma is usually of no clinical significance. However, the tumors may enlarge and cause the mucosa to ulcerate and thus give clinical signs; transformation into leiomyosarcoma seems possible.

5. Lahey, F. H., and Colcock, B. P.: *Ann. Surg.* **112**:671, 1940.

3. Rieniets, J. H.: *Proc. Staff Meet., Mayo Clin.* **5**:364, 1930.

4. Borrmann, R.: *Geschwülste des Magens und Duodenums*, in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 4, pt. 1, p. 812.

## EXPERIMENTAL ATHEROSCLEROSIS

### VI. EFFECTS OF VARIOUS BILE ACIDS ON CHOLESTEROL LEVELS

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The manner in which fats are absorbed from the intestinal tract has long been a controversial subject. Although it is agreed that neutral fat is hydrolyzed by lipase prior to absorption,<sup>1</sup> the nature of the processes by which fatty acids, insoluble in water, are brought into solution and transported across the intestinal wall is not clearly understood. At first it was assumed that the insoluble fatty acids combined with the alkaline pancreatic juice to form soaps and as such diffused into the intestinal epithelium. It has recently been shown, however, that the intestinal contents are slightly acid in reaction; the role of the bile salts and bile acids in the absorption of fat has therefore attracted renewed attention.

According to Verzár and von Kuthy,<sup>2</sup> during the digestion of fat the bile salts and acids become adsorbed to the intestinal epithelium and by virtue of their hydrotropic action are able to attract and pass the fatty acids into the epithelial cells. These workers found bile salts to be good solvents for oleic, palmitic and stearic acids. Fürth and Scholl<sup>3</sup> reported that both saponified and nonsaponified fats require bile for their absorption from the intestines. Riegel and his co-workers<sup>4</sup> studied the absorption of oleic acid in intestinal loops of dogs and showed that the absorption of this fatty acid was greatly increased in the presence of sodium taurocholate in the loop and somewhat less increased in the presence of hepatic or gallbladder bile. They ascribed the action of taurocholate to surface phenomena since minute concentrations of the bile salt facilitated the absorption of relatively large amounts of fatty acid.

Another hypothesis which deserves mention is the so-called "choleic acid principle" proposed by Wieland and Sorge.<sup>5</sup> They found that desoxycholic acid formed stable water-soluble molecular compounds with higher fatty acids and cholesterol and ascribed an important function to this phenomenon in the transporting of insoluble substances through the intestinal wall. Bashour and Bauman<sup>6</sup> studied the solubility of cholesterol in various solutions of bile salts; cholesterol was found to be most soluble in solutions of desoxycholate and least soluble in those of taurocholate. Spanner and Bauman<sup>7</sup> had shown previously that sodium desoxycholate was the most effective of the bile salts studied in keeping cholesterol in solution. The addition of sodium oleate to desoxycholate almost doubled its solvent properties for cholesterol. Likewise, Schönheimer<sup>8</sup> found that desoxycholic acid hastens the absorption of cholesterol from the intestinal tract of mice and rabbits.

Nedswedski<sup>9</sup> found that in the presence of bile salts, cholesterol may be esterified with palmitic, stearic or oleic acids by the action of lipase. Frölicher and Süllmann<sup>10</sup> noted that in rabbits fed cholesterol, free and combined cholesterol in the intestinal lymph rose to about the same extent, indicating that partial esterification of free cholesterol takes place in the intestinal wall. Hummel<sup>11</sup> reported that while bile acids fed to mice caused a moderate increase in the cholesterol content of the liver, the simultaneous feeding of bile salts and cholesterol resulted in considerable deposition of this sterol

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1. Fat Absorption, editorial, *J. A. M. A.* **105**:122, 1935.

2. Verzár, F., and von Kuthy, A.: *Biochem. Ztschr.* **205**:369, 1929; **210**:265 and 281, 1929; **225**:267, 1930; **230**:451, 1931.

3. Fürth, O., and Scholl, R.: *Biochem. Ztschr.* **222**:430, 1930.

4. Riegel, C.; Elsom, K., and Ravdin, I. S.: *Am. J. Physiol.* **112**:669, 1935.

5. Wieland, H., and Sorge, H.: *Ztschr. f. physiol. Chem.* **97**:1, 1916.

6. Bashour, J. T., and Bauman, L.: *J. Biol. Chem.* **121**:1, 1937.

7. Spanner, G. O., and Bauman, L.: *J. Biol. Chem.* **98**:181, 1932.

8. Schönheimer, R.: *Biochem. Ztschr.* **147**:258, 1924.

9. Nedswedski, S. W.: *Ztschr. f. physiol. Chem.* **236**:69, 1935.

10. Frölicher, E., and Süllmann, H.: *Biochem. Ztschr.* **274**:21, 1934.

11. Hummel, R.: *Ztschr. f. physiol. Chem.* **185**:105, 1929.

in the liver. Loeffler<sup>12</sup> described somewhat similar results in mice and also concluded that greater storage of lipid occurs in the liver when bile acids are fed along with cholesterol.

The primary purpose of the present investigation was to determine the effect of a selected bile acid when fed with cholesterol on the level of the blood cholesterol and on the amount of this sterol deposited in the aorta. Additional data on the cholesterol content of the liver were also obtained in two experiments.

#### MATERIAL AND METHODS

In all, 75 female rabbits, 3 to 5 months old, were used in this study. Thirty-nine served as controls. Each animal was fed a basic ration of Ralston Purina rabbit chow<sup>13</sup> daily and 1 Gm. of cholesterol was mixed with the food three times weekly for a period

The bile acids were investigated consecutively rather than concurrently because of lack of animal space. For each group of experimental animals studied, a control series was examined simultaneously; the total duration of the experiment was therefore sixty-six weeks.

The total and the ester cholesterol in the whole blood were determined at regular intervals by a modified Bloor method.<sup>15</sup> At the end of the experimental period (twelve to fourteen weeks), the rabbits were killed. The procedure used for killing the animal, removing the aorta and determining its cholesterol content has been described elsewhere.<sup>16</sup> In two experiments the cholesterol content of the liver was also estimated.

#### RESULTS

*Dehydrocholic Acid.*—Table 1 shows the results obtained with this bile acid. For each two week period, the total cholesterol in the whole blood was moderately higher in the experimental group (average 675 mg. per hundred cubic centimeters at the fourteenth week) as

TABLE 1.—Effect of Feeding Cholesterol With and Without Simultaneous Feeding of Dehydrocholic Acid on the Total and the Ester Cholesterol Content of the Whole Blood and on the Cholesterol Content of the Aorta

Rabbit No.	Cholesterol in Whole Blood												Cholesterol in Aorta, Mg. per 100 Gm. Dry Weight
	Total, Mg. per 100 Ce.								Esters, % of Total				
	0 Wk.	2 Wk.	4 Wk.	6 Wk.	8 Wk.	10 Wk.	12 Wk.	14 Wk.	0 Wk.	4 Wk.	8 Wk.	14 Wk.	
Control Group—1 Gm. of Cholesterol Three Times Weekly for Fourteen Weeks													
12	96	114	121	101	371	625	564	636	10	19	51	59	614
13	99	148	130	188	536	472	441	586	15	32	47	48	656
14	72	107	177	280	387	625	507	493	15	25	49	63	1,751
15	96	101	105	235	441	521	472	625	12	18	54	52	563
17	136	163	199	487	559	595	455	412	21	..	51	67	1,374
21	85	123	214	521	487	417	452	528	13	35	50	71	1,511
25	95	...	295	457	559	494	306	296	14	45	51	54	1,648
26	96	...	452	493	487	893	815	658	18	50	45	73	4,589
Average	98	126	212	345	479	581	512	529	13	32	49	61	1,588
Experimental Group—1 Gm. of Cholesterol and 0.5 Gm. of Dehydrocholic Acid Three Times Weekly for Fourteen Weeks													
1	164	155	200	164	457	595	484	507	31	20	51	58	793
2	84	341	318	670	516	707	606	700	15	32	66	43	2,391
3	90	103	89	190	156	395	452	514	12	23	31	65	811
4	107	139	193	252	156	291	344	500	19	..	39	53	946
7	125	131	202	463	383	494	401	431	20	31	48	61	310
9	121	451	551	735	1,042	1,271	1,316	1,200	19	51	60	52	1,809
10	89	191	383	670	884	987	1,042	875	14	31	54	71	3,354
Average	112	220	277	449	509	677	664	675	19	31	50	58	1,488

varying from twelve to fourteen weeks. Thirty-six rabbits received in addition to the chow and cholesterol 0.5 Gm. of dehydrocholic acid, cholic acid, hydesoxycholic acid (whole hog bile), desoxycholic acid or glycocholic acid<sup>14</sup> three times weekly. The bile acid was also mixed intimately with the chow, especial care being exercised that the rabbits consumed their ration of cholesterol and bile acid completely.

12. Loeffler, K.: *Ztschr. f. physiol. Chem.* **178**:186, 1928.

13. This chow contains a mixture of grains and alfalfa hay supplemented by vitamins and minerals.

14. The dehydrocholic acid was obtained from E. R. Squibb & Sons, the cholic acid from Sandoz Chemical Works, Inc., the hydesoxycholic acid (whole hog bile) from Parke, Davis & Company and the desoxycholic acid and glycocholic acid from Sandoz Chemical Works, Inc. and from the private stocks of Dr. Carl H. Greene. The glycocholic acid fed was a mixture of equal parts of the free acid and sodium glycocholate. The material supplied by Dr. Greene was made by C. H. Boehringer Sohn, Germany.

compared with the controls (average 529 mg. per hundred cubic centimeters at the fourteenth week). The rate of increase of ester cholesterol in the whole blood was similar in both groups. Little or no difference was observed in the amount of cholesterol deposited in the aorta in control and in experimental animals.

*Cholic Acid.*—The results obtained with this bile acid are given in table 2. In rabbits receiving cholic acid and cholesterol, not only was the concentration of total cholesterol in the whole blood significantly higher (average 649 mg. per hundred cubic centimeters, compared with 401 mg. per hundred cubic centimeters in the controls, at the fourteenth week), but the per cent of ester cholesterol in the blood was greater than in rabbits fed cholesterol alone (43 per cent in the experimental group compared with 30 per cent in the controls at the eighth week). Moreover, considerably more cholesterol was deposited in the aorta in rabbits

15. Bloor, W. R., and Knudson, A.: *J. Biol. Chem.* **27**:107, 1916.

16. Bruger, M., and Fitz, F.: *Arch. Path.* **25**:637, 1938.

fed cholic acid (average 3,389 mg. per hundred grams of dry aorta in the experimental group compared with 1,398 mg. per hundred grams of dry aorta in the controls).

It may be of interest to mention that at necropsy the gallbladders of the rabbits fed cholic acid and cholesterol were considerably enlarged. The control animals showed no such change. Histologic studies of these

deposit of this sterol in the aorta than was the feeding of cholesterol alone.

*Desoxycholic Acid.*—The results obtained with this bile acid are given in table 4. Like hyodesoxycholic acid, desoxycholic acid was without influence on the cholesterol content of the whole blood or on that of the aorta. This bile acid did not increase the cholesterol content of the liver.

TABLE 2.—Effect of Feeding Cholesterol With and Without Simultaneous Feeding of Cholic Acid on the Total and the Ester Cholesterol Content of the Whole Blood and on the Cholesterol Content of the Aorta

Rabbit No.	Cholesterol in Whole Blood										Cholesterol in Aorta, Mg. per 100 Gm. Dry Weight
	Total, Mg. per 100 Cc.						Esters, % of Total				
	0 Wk.	2 Wk.	4 Wk.	6 Wk.	8 Wk.	14 Wk.	0 Wk.	4 Wk.	8 Wk.	14 Wk.	
Control Group—1 Gm. of Cholesterol Three Times Weekly for Fourteen Weeks											
111	89	96	276	262	150	605	8	34	17	53	2,303
112	111	313	408	906	500	682	9	45	31	44	721
113	120	375	347	384	347	664	10	38	41	34	1,061
114	134	188	148	423	280	145	8	21	28	31	1,061
115	98	375	323	750	544	620	9	33	42	53	4,855
116	95	195	357	245	250	364	7	42	23	51	500
117	115	375	278	250	255	185	8	35	29	35	981
118	94	202	150	129	168	305	8	34	27	52	884
119	102	206	213	388	107	107	9	38	31	24	1,082
120	85	112	217	352	239	240	7	29	29	47	531
Average	104	244	272	409	279	401	8	35	30	42	1,398
Experimental Group—1 Gm. of Cholesterol and 0.5 Gm. of Cholic Acid Three Times Weekly for Fourteen Weeks											
102	90	605	1,108	1,136	987	750	10	56	43	48	4,700
103	79	276	507	750	815	806	8	42	50	47	2,731
104	121	625	815	688	815	652	7	55	51	43	4,437
105	82	363	341	707	586	538	6	42	43	55	1,662
106	117	625	875	1,102	873	615	13	47	42	47	5,682
107	106	329	473	595	247	324	8	45	29	51	1,440
109	107	625	660	1,000	962	806	11	44	53	49	5,621
110	104	507	213	433	391	707	8	25	33	58	837
Average	103	506	622	801	710	640	9	45	43	49	3,389

TABLE 3.—Effect of Feeding Cholesterol With and Without Simultaneous Feeding of Hyodesoxycholic Acid (Whole Hog Bile) on the Total and the Ester Cholesterol Content of the Whole Blood and on the Cholesterol Content of the Aorta

Rabbit No.	Cholesterol in Whole Blood										Cholesterol in Aorta, Mg. per 100 Gm. Dry Weight
	Total, Mg. per 100 Cc.					Esters, % of Total					
	0 Wk.	3 Wk.	6 Wk.	9 Wk.	12 Wk.	0 Wk.	3 Wk.	6 Wk.	9 Wk.	12 Wk.	
Control Group—1 Gm. of Cholesterol Three Times Weekly for Twelve Weeks											
211	96	240	173	670	781	16	34	29	42	47	951
212	94	368	561	987	833	16	38	44	41	51	2,229
214	71	114	...	750	708	18	25	..	38	41	1,843
216	114	148	245	750	915	18	31	31	50	54	1,376
218	89	144	100	694	750	14	26	31	54	45	814
220	100	350	371	551	708	15	32	35	41	43	790
Average	94	227	307	734	783	16	31	34	44	47	1,334
Experimental Group—1 Gm. of Cholesterol and 0.5 Gm. of Hyodesoxycholic Acid Three Times Weekly for Twelve Weeks											
201	87	184	551	1,042	803	18	28	40	50	53	1,292
202	98	226	315	658	781	16	26	34	50	56	1,261
206	108	235	514	605	...	18	37	39	34	..	1,560*
204	93	313	475	507	647	23	28	42	41	44	1,142
206	89	798	387	568	750	22	36	38	40	46	1,506
207	107	175	208	...	...	21	28	35	...	...	566†
Average	97	322	408	676	766	20	31	38	43	50	1,221

\* The rabbit died at the eleventh week.  
† The rabbit died at the tenth week.

enlarged gallbladders made by Dr. Henry Spitz, of the Department of Pathology of the New York Post-Graduate Medical School and Hospital, showed pronounced thickening of the wall.

*Hyodesoxycholic Acid (Whole Hog Bile).*—Table 3 details the results obtained with hyodesoxycholic acid. The feeding of this bile acid and cholesterol was accompanied by no greater concentration of total or of ester cholesterol in the whole blood and by no greater

*Glycocholic Acid.*—Table 5 details the findings with glycocholic acid. Like cholic acid, glycocholic acid when fed simultaneously with cholesterol augmented markedly the total cholesterol content of the whole blood (average 1,054 mg. per hundred cubic centimeters in the experimental group, compared with 576 mg. per hundred cubic centimeters in the controls at the eighth week) and of the aorta (average 4,799 mg.

per hundred grams of dry aorta in the experimental group, compared with 2,932 mg. per hundred grams of dry aorta in the controls). The percentage of ester cholesterol in the whole blood appeared to be influenced little by this bile acid. The ingestion of glycocholic acid and cholesterol resulted in a pronounced deposition of cholesterol in the liver in experimental rabbits

aorta (feeding of cholesterol without bile acid was the control). Dehydrocholic acid, hydoxycholic acid and desoxycholic acid do not possess this property. Moreover, in a limited study it was shown that the ingestion of glycocholic acid and cholesterol is followed by

TABLE 4.—Effect of Feeding Cholesterol With and Without Simultaneous Feeding of Desoxycholic Acid on the Total and the Ester Cholesterol Content of the Whole Blood and on the Cholesterol Content of the Aorta and of the Liver

Rabbit No.	Cholesterol in Whole Blood										Cholesterol in Aorta, Mg. per 100 Gm. Dry Weight	Cholesterol in Liver, Mg. per 100 Gm. Wet Weight
	Total, Mg. per 100 Ce.					Esters, % of Total						
	0 Wk.	3 Wk.	7 Wk.	11 Wk.	13 Wk.	0 Wk.	3 Wk.	7 Wk.	11 Wk.	13 Wk.		
Control Group—1 Gm. of Cholesterol Three Times Weekly for Thirteen Weeks												
312	81	147	781	917	586	21	48	43	47	43	745	631
316	96	225	550	412	481	19	50	31	30	38	1,207	958
317	76	139	347	221	508	16	49	38	51	44	648	558
318	96	431	813	1,136	908	21	55	56	48	53	1,023	782
319	121	506	823	682	852	17	61	42	48	36	1,196	815
320	99	431	750	1,250	1,250	21	47	44	43	39	647	928
Average	95	328	681	770	779	19	51	42	45	42	1,061	762
Experimental Group—1 Gm. of Cholesterol and 0.5 Gm. of Desoxycholic Acid Three Times Weekly for Thirteen Weeks												
301	142	332	765	873	1,072	31	54	46	45	..	853	876
302	100	460	625	...	682	27	42	35	..	47	957	406
303	117	403	508	833	721	25	44	45	51	39	600	1,309
305	119	260	765	682	908	24	48	47	42	32	734	1,077
307	125	403	625	708	577	30	51	39	37	46	985	988
308	107	399	908	815	682	26	54	43	49	41	3,125	750
309	100	815	586	457	...	25	51	53	45	..	631	605
311	120	255	682	...	694	26	40	38	..	42	931	462
322	118	149	332	...	190	25	36	52	..	42	633	392
Average	116	387	654	728	695	26	47	44	45	41	1,047	756

TABLE 5.—Effect of Feeding Cholesterol With and Without Simultaneous Feeding of Glycocholic Acid on the Total and the Ester Cholesterol Content of the Whole Blood and on the Cholesterol Content of the Aorta and of the Liver

Cholesterol in Whole Blood															Cholesterol in Aorta, Mg. per 100 Gm. Dry Weight	Cholesterol in Liver, Mg. per 100 Gm. Wet Weight
Rabbit No.	Total, Mg. per 100 Ce.							Esters, % of Total								
	0 Wk.	2 Wk.	4 Wk.	6 Wk.	8 Wk.	10 Wk.	13 Wk.	0 Wk.	2 Wk.	4 Wk.	6 Wk.	8 Wk.	10 Wk.	13 Wk.		
Control Group—1 Gm. of Cholesterol Three Times Weekly for Thirteen Weeks																
511	100	175	344	361	658	902	872	..	..	..	..	..	..	..	2,641	690
520	190	300	250	217	283	242	506	..	..	..	..	..	..	..	645	452
532	110	383	550	908	815	893	625	21	54	46	51	50	48	40	9,615	943
533	105	222	391	326	417	658	658	17	39	47	23	42	50	30	1,645	1,009
534	137	290	500	596	682	765	833	25	37	44	40	41	42	41	2,840	642
535	99	305	347	417	750	1,108	1,103	34	54	44	47	41	41	51	3,375	599
536	127	341	178	154	278	290	296	22	55	53	47	50	36	38	934	442
539	99	371	625	670	625	987	1,136	25	41	62	38	50	47	36	3,538	723
540	85	297	296	421	708	551	...	22	49	66	47	51	29	..	1,156	1,116
Average	110	283	384	455	576	714	761	24	47	50	42	46	42	39	2,932	726
Experimental Group—1 Gm. of Cholesterol and 0.5 Gm. of Glycocholic Acid Three Times Weekly for Thirteen Weeks																
522	98	210	436	689	858	735	735	26	54	54	51	44	43	49	5,953	1,219
523	123	183	115	765	1,339	962	967	29	53	50	44	49	39	34	2,568	1,275
534	199	431	417	731	852	1,100	...	43	44	46	44	35	..	..	8,000	1,303
539	211	606	998	1,014	1,500	1,014	815	38	56	45	48	43	31	35	3,720	1,674
541	117	276	294	323	1,072	...	...	19	48	32	39	43	..	..	757	1,629
543	131	132	433	383	708	852	893	29	38	48	46	43	34	49	7,796	580
Average	136	346	397	648	1,054	933	858	31	49	46	45	43	37	42	4,796	1,375

(average 1,375 mg. per hundred grams of wet liver) compared with animals fed cholesterol alone (average 726 mg. per hundred grams of wet liver).

#### COMMENT

The foregoing experiments on rabbits indicate that feeding of cholic acid or glycocholic acid and cholesterol increases markedly the cholesterol content of the whole blood and of the

deposition of large amounts of cholesterol in the liver whereas desoxycholic acid produces no such result. Again, feeding of cholic acid, unlike that of the other bile acids tested, is accompanied by increased concentration of combined (ester) cholesterol in the whole blood; it is conceivable that cholic acid may stimulate esterification of cholesterol in the wall of the gut.

Cholic acid and glycocholic acid probably increase the absorption of cholesterol from the intestinal tract, thus producing high concentrations of this sterol in the blood. The deposition of cholesterol in the aorta and (as shown in the experiment with glycocholic acid) in the liver is thereby enhanced. It is interesting to note that the other bile acids tested produce no such effects.

This selective action on cholesterol metabolism of some of the bile acids may be gleaned from the *in vitro* experiments of Bauman and his co-workers<sup>17</sup>; these investigators noted that the solubility of cholesterol was different in various solutions of bile salts. Loeffler<sup>12</sup> found in mice that the liver contained greater concentrations of cholesterol when cholic acid was fed as compared with the levels obtained after the feeding of desoxycholic acid. Hummel<sup>11</sup> subsequently

confirmed these observations, using cholic acid; dehydrocholic acid was shown to have no such effect.

#### SUMMARY

Cholic or glycocholic acid fed with cholesterol to the rabbit increases markedly the cholesterol contents of the whole blood and the aorta as compared with the levels obtained following the ingestion of cholesterol alone.

Dehydrocholic acid, hyodesoxycholic acid and desoxycholic acid do not possess this property.

In two series of experiments in which desoxycholic acid and glycocholic acid were used respectively, the latter was shown to augment the cholesterol content of the liver; the former was without effect in this regard.

The feeding of cholic acid, unlike that of any other bile acid tested, is accompanied by increased concentration of combined (ester) cholesterol in the whole blood.

17. Bashour and Bauman.<sup>6</sup> Spanner and Bauman.<sup>7</sup>

# EFFECT OF 3,4-BENZPYRENE ON REGENERATING EPIDERMIS OF MICE

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The regeneration of the skin of mice painted with the carcinogenic substance 3,4-benzpyrene previous to the making of a wound differed from that of normal epidermis in various respects<sup>1</sup>: It was accelerated if the duration of the treatment did not exceed one month; it was delayed if the treatment was continued for periods of two to three months prior to excision. The retardation resulted from an inhibition of the migration of the epithelial cells from the periphery toward the center of the defect. This inhibition was the more striking since growth processes in the epidermis were invariably stimulated under the influence of benzpyrene. The cause of this change could not be determined definitely; but the possibility was considered that the interference was due to alterations in the epithelium or in the base of the wound.

The present investigation was undertaken in order to find out whether or not regeneration of the epidermis takes a similar course if benzpyrene is applied to a wound made in normal skin.

## MATERIAL AND METHODS

Twenty-eight white Swiss mice, 6 to 8 weeks old, were divided into three groups, litter mates being equally distributed whenever possible. The animals were kept on a diet of Purina checkers and water, both available at all times. The hair over the lower part of the back of each mouse was carefully clipped, and a circular piece of skin measuring 7 mm. in diameter was excised with a pair of curved scissors. Regeneration was allowed to take place for three, five, eight, eleven, fourteen, twenty-one or twenty-eight days.

*First Group (7 animals).*—In this series the wounds were allowed to heal spontaneously.

*Second Group (7 animals).*—In this series of wounds and the surrounding skin were painted with the solvent, benzene.

*Third Group (14 animals).*—In this series a 0.3 per cent solution of 3,4-benzpyrene in benzene was applied to each wound and the surrounding skin by one stroke with a camel's hair brush, no. 6, previously dipped into the solution of benzpyrene. This was done for the

first time immediately after the making of the wound; it was repeated every other day with the exception of Sundays.

At the end of the experimental period, the mice were killed with chloroform between 10 and 11 a. m. A piece of skin including the wound was taken out and stretched on filter paper, and the diameter of the wound was measured with a caliper; then the specimen was fixed in a 4 per cent solution of formaldehyde, embedded in paraffin, sectioned and stained with hematoxylin and eosin. The details of the method used in the histologic examination are the same as those given by Loeb<sup>2</sup> in his work on the regeneration of the skin. Briefly, the following areas are described separately: (1) the old epithelium at some distance from the wound, as well as that immediately adjacent to the line of excision; (2) the regenerating epithelium, in which likewise two areas are distinguished—the elongated epithelial tongue advancing from the periphery toward the center of the defect and its broad-based insertion at the old epithelium.

TABLE 1.—Diameter of the Wounds at the End of the Experimental Period\*

Duration of Experiment (Days)	Diameter (Millimeters) in			
	Normal Animals	Benzene-Treated Animals	Benzpyrene-Treated Animals	
3	5.5 × 5.5	5.5 × 5.5	6.5 × 6.5	6.0 × 6.0
5	6.0 × 6.0	4.5 × 4.5	3.0 × 6.0	4.0 × 5.0
8	5.0 × 5.0	2.7 × 2.7	2.7 × 4.0	3.7 × 4.0
11	1.2 × 1.2	Closing	0.5 × 0.5	0.5 × 0.5
14	0.5 × 0.5	Closing	Closing	Closing
21	Closed	Closed	Closed	Closed
28	Closed	Closed	Closed	Closed

\* In most of the animals the margins of the wound retracted somewhat after excision.

The length of the advancing tongue was measured with an object micrometer; the values are given in column 6, tables 2, 3 and 4. The number of cell rows (columns 3 to 5, tables 2 to 4) and the number of mitoses (columns 7 and 8, tables 2 to 4) were determined. As in a previous investigation,<sup>1</sup> the mitotic count is given in multiples of the normal, the means and the maximum and minimum deviations being indicated.

## OBSERVATIONS ON THE FIRST GROUP OF MICE

The mice in the first group were control mice, not treated with benzene or benzpyrene.

*Gross Examination.*—The scab covering the wound decreased in size with increasing duration of the experiment. Fourteen days subsequent to operation a scab less than 1 mm. in diameter was present.

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1. Silberberg, M., and Silberberg, R.: *Am. J. Path.* 20:809, 1944.

2. Loeb, L., and Addison, W. H. F.: *Arch. f. Entwicklungsmechn. d. Organ.* 32:44, 1911; 37:635, 1913.

**Histologic Examination.**—(a) Old Epithelium: At a distance from the wound the skin consisted of two rows of epithelial cells. The upper layer was composed of elongated keratinizing spinous cells; the deeper one of ellipsoid basal cells. The ratio of basal to spinous cells was 2:1 or 3:1. There were 12 mitoses on the average in 10,000 basal cells, the maximum being 14 and the minimum 9 in 10,000.

Three and five days after operation, the epithelium at the margin of the wound was thickened, and the spinous cells were markedly keratinized. The basal cells were 35 to 45 per cent larger than ordinarily; they were cylindric in shape and had arranged themselves in a direction perpendicular to the surface. The nuclei were likewise enlarged and stained more lightly with hematoxylin than usual; the nucleoli had become indistinct. Mitotic division of the basal cells was increased and had reached a maximum of seven times the normal five days subsequent to excision of the piece of skin (table 2, column 7).

From eight to fourteen days after operation, the basal cells were less hypertrophic than after three and five

which is only insignificantly greater than the normal number of two.

In the tongue proper the cells were stretched out, the more so the closer they were situated to the tip. From three to eight days after operation the tongue consisted of two to four rows of hypertrophic epithelial cells (table 2, column 5), which were 30 to 50 per cent larger than ordinarily. After eleven and fourteen days the tongues had reached their maximum thickness of four to five cell rows. At later stages, when the wound had closed, there were again two or three cell rows (table 2, column 5).

The mitotic count in the new epithelium (table 2, column 8) had reached its peak eleven to fourteen days after operation. It was then increased on the average three and one-half times, with a maximum of seven and a minimum of three times the normal. From then on, the mitotic count approached more and more the normal, which finally occurred at about the end of the third week of observation.

#### OBSERVATIONS ON THE SECOND GROUP: MICE PAINTED WITH BENZENE

**Gross Examination.**—After one and two weeks of application of benzene, and even more after three and four weeks, the skin around the wound had undergone thickening and more marked keratinization than normal. During the first week the wound gradually decreased in size. Eight days after excision the defect had a diameter of 2.75 by 2.75 mm. only, compared with 5.0 by 5.0 mm. in the corresponding untreated animal (table 1, column 2); after eleven days the wound was closed and showed scarring, whereas in the control animal a defect measuring 1.2 by 1.2 mm. was still visible at this stage. Thus repair was hastened under the influence of benzene.

**Histologic Examination.**—(a) Old Epithelium: With increasing duration of the application of benzene, the epidermis at a distance from the wound became somewhat thicker (table 3, column 3). After two weeks of treatment it consisted of two or three cell rows instead of the usual two. The number of epidermal cells increased about 30 per cent, and mitotic proliferation of the basal cells was slightly increased if the mitoses were counted per unit area. However, if the mitoses were counted in a given number of basal cells, the mitotic index was normal. The number of spinous cells was relatively more increased than that of the basal cells, the ratio of basal to spinous cells having changed to 1.8:1, compared with 2:1 or 3:1 in the control animals. Keratinization of the epidermis was marked, and here and there pearls of keratin were found in the surface epithelium. The subcutis showed mild infiltration by polymorphonuclear and mononuclear leukocytes.

In the epithelium at the margin of the wound the basal cells were even larger than those in the control mice; their hypertrophy became more marked with increasing duration of the treatment. The largest basal cells were almost twice as large as normal basal cells. As in the untreated animals, the thickness of the epidermis increased toward the edge of the excision. Mitotic proliferation of the basal cells was accentuated; the maximum was found as early as three days after operation, whereas in the control mice the peak was reached after five days (tables 2 and 3, column 7). Eight days after excision the number of mitoses was still five times the normal, whereas in the control mice the number was only two and one-half times higher than that in the resting epidermis. After painting with

TABLE 2.—Control Animals

Days After Excision	Mouse No.	Cell Rows in		Tongue	Length of Tongue in Mm.	Mitoses in Multiples of the Normal	
		Old Epithelium (Distal)	Insertion of Tongue			Old Epithelium (Marginal)	New Epithelium
3	100	2	5-6	2-3	0.28	3 max. 5 min. 2½	0
5	101	2	5	4	0.39	6 max. 7 min. 3½	3 max. 4 min. 2
8	105	2	4-5	3-4	0.53	2½ max. 3½ min. 1	3 max. 5 min. 2
11	113	2	4-5	4-5	0.85	2 max. 3 min. 1	3½ max. 6 min. 3
14	117	2	5	4-5	1.15	1½ max. 2½ min. 1	3½ max. 7 min. 3
21	121	2	2-3	3	Closed	1 max. 1 min. 1	2 max. 3 min. 1
28	125	2	2-3	2-3	Closed	1 max. 1 min. 1	1 max. 1 min. 1

days, but they were still 20 to 30 per cent larger than usual. Their mitotic proliferation began to decline but still remained elevated. Twenty-one and twenty-eight days subsequent to excision, a return to the resting state had taken place (table 2, column 7), and the marginal epithelium could no longer be distinguished from the epithelium that was farther away from the line of excision. The basal cells had assumed the usual size; the nuclei again stained deeply with hematoxylin, and the nucleoli were definite. Only the keratinization of the spinous cells continued to be pronounced.

(b) New Epithelium: During the first fourteen days subsequent to operation, enlarged epithelial cells were seen to grow out in a tongue from the margin of the wound under the blood clot that covered the defect of the skin; the length of the advancing tongue increased gradually with increasing duration of the experiment (table 2, column 6). After three and four weeks the tongues moving toward the center from both sides joined and thus closed the defect.

At its insertion the regenerating epithelial tongue was thick. During the first two weeks it consisted of four to six cell rows (table 2, column 4). Later the epithelium was composed of two to three cell rows,

benzene for two weeks the mitotic count was normal in proportion to the number of basal cells, although it was elevated over the normal in any given area. In the control animals, on the other hand, the mitotic index was still absolutely and relatively increased.

(b) *New Epithelium*: At any given stage the tongues were longer in the benzene-treated animals than in the control mice (tables 2 and 3, column 6). Three days after the excision of skin the tongues measured 0.35 mm. in the former and only 0.28 mm. in the latter animals; after five days the corresponding figures were 0.52 mm. and 0.39 mm., respectively, and after eight days they were 0.88 mm. and 0.53 mm. After eleven days' application of benzene the tongues began to join, whereas in the controls they measured 0.85 mm. and had not yet met. After fourteen days the wounds were closed under the influence of benzene, while in the untreated animals the tongues measured 1.15 mm. and had not yet completely covered the defect.

From three to eleven days subsequent to operation the epithelium at the insertion of the tongue was somewhat thicker (five to seven cell rows) than that in the

days of treatment. The closure of the wounds was accelerated as compared with that observed in the control mice of the first group and resembled that seen after application of benzene (table 1). The defects were almost closed after fourteen days of painting with benzpyrene.

*Histologic Examination.*—(a) *Old Epithelium*: The epidermis distant from the defect was thicker than in either the control mice or the animals painted with benzene (tables 2 to 4, column 3). After two weeks it was composed of three to four cell rows as contrasted with two to three rows in the benzene-treated and two rows in the untreated animals. Subsequently, the thickness of the epithelium increased still further (three to five rows). The markedly hypertrophic basal cells were 20 to 25 per cent larger than those in the

TABLE 3.—Animals Treated with Benzene

Days After Excision	Mouse No.	Cell Rows in			Length of Tongue in Mm.	Mitoses in Multiples of the Normal	
		Old Epithelium (Distant)	Insertion of Tongue	Tongue		Old Epithelium (Marginal)	New Epithelium
3	110	2	5-6	3-4	0.35	7½ max. 8 min. 6	3 max. 3 min. 1
5	102	2	5-6	3-4	0.52	6½ max. 8 min. 5	5½ max. 8 min. 4
8	106	2-3	6-7	4-5	0.88	5 max. 6½ min. 3½	5 max. 6 min. 4
11	114	2	5-6	3-4	Closed	2 max. 2 min. 1	1½ max. 2 min. 1
14	118	2-3	2-3	4-5	Closed	1 max. 1 min. 1	1 max. 1 min. 1
21	122	2-3	2-3	3-4	Closed	1 max. 1 min. 1	1 max. 1 min. 1
28	126	2-3	2-3	3	Closed	1 max. 1 min. 1	1 max. 1 min. 1

control mice (four to six cell rows). The tongue itself consisted of three to five rows of cells; conditions thus resembled those in the control group (two to five rows of cells). After two weeks the epidermis covering the former site of the wound was composed of two to three cell rows, whereas in the control series this condition was reached only after three weeks.

In the benzene-treated mice the mitotic count was five and a half times the normal five days subsequent to operation, when it reached its peak (table 3, column 8); in the untreated animals the mitotic index was only three and a half times the normal, and its maximum was seen toward the end of the second week. Fourteen days after excision the mitoses in the benzene group had returned to normal, a condition observed in the untreated mice during the fourth week only.

## OBSERVATIONS ON THE THIRD GROUP:

## MICE PAINTED WITH BENZPYRENE

*Gross Examination.*—With increasing duration of treatment, the epidermis underwent thickening and keratinization. The keratin frequently peeled off in large scales. In six of eight animals the skin around the excision had become epilated after eleven and more

TABLE 4.—Animals Treated with Benzpyrene

Days After Excision	Mouse No.	Cell Rows in			Length of Tongue in Mm.	Mitoses in Multiples of the Normal	
		Old Epithelium (Distant)	Insertion of Tongue	Tongue		Old Epithelium (Marginal)	New Epithelium
3	111	2	5-6	3-4	0.31	7½ max. 8½ min. 6½	3 max. 3 min. 2
3	112	2	6	3-4	0.38	8 max. 11 min. 7	3½ max. 4 min. 2
5	103	2-3	4-5	3	0.58	8½ max. 10 min. 7	5 max. 8 min. 4
5	104	2	2-3	2	0.46	9½ max. 3½ min. 1½	3 max. 5 min. 2
8	107	2	7-8	0-7	0.53	10 max. 11 min. 8	10 max. 11 min. 5
8	108	2-3	8-9	0-7	0.50	10 max. 12½ min. 8	10 max. 11 min. 6
11	115	2-3	8-0	0-7	1.12	4 max. 5 min. 3	8 max. 9 min. 6
11	116	3-4	4-5	0-7	1.10	4 max. 5½ min. 2½	10 max. 12 min. 7
14	119	3-4	3-4	3-4	Closed	4 max. 5 min. 3½	10 max. 12 min. 9
14	129	3-4	4	3-4	Closed	4 max. 5 min. 8	19 max. 12 min. 8
21	123	3-4	3-4	0-7	Closed	6 max. 7½ min. 5	7½ max. 8 min. 6
21	124	3-4	3-4	7-8	Closed	4 max. 5½ min. 2½	5½ max. 6 min. 4
28	127	4-5	4-5	4-5	Closed	5½ max. 7½ min. 4	5½ max. 7½ min. 4
28	128	3-4	3-4	3-4	Closed	5 max. 7 min. 4½	5 max. 7 min. 4½

corresponding benzene-treated mice. The ratio of basal to spinous cells had shifted more and more in favor of the latter. After two weeks of painting it was 1:1, and after four weeks of treatment it was 1:1.4. The basal cells proliferated actively, and not infrequently the nuclei underwent pyknosis, karyolysis or karyorrhexis. There were scattered foci of polymorphonuclear and mononuclear leukocytes in the subcutis; pearls of keratin were found in the deeper layers of the spinous cells. The hair follicles likewise were frequently filled with keratin. The subcutaneous tissue was edematous; the collagen fibrils were swollen, delicate and often fragmented. Here and there, infiltration by polymorphonuclear leukocytes was noticeable.

Hypertrophy and hyperplasia of the epidermal cells were even more accentuated close to the margin of the excision. As early as three days after operation the mitoses had multiplied six and a half to eleven fold. This compares with the highest mitotic index of seven

times the normal in untreated mice, observed five days after excision, and with the maximum of eight times the normal noted three and five days subsequent to operation in the benzene-treated animals (tables 2 to 4, column 7). Eight days after excision the mitotic count was even more elevated (eight to twelve and a half times) and higher than the peak of proliferation observed in either the benzene-treated or the control group. After fourteen days the mitotic index dropped sharply to four times (mean) the normal but remained high throughout the period of observation.

(b) New Epithelium: After three days of treatment with benzpyrene the tongues measured 0.31 mm. and 0.38 mm., compared with 0.35 mm. in the benzene-treated and 0.28 mm. in the control mice. After five days the corresponding figures were 0.58 mm. and 0.46 mm. for the benzpyrene-treated mice, 0.52 mm. for the benzene-treated and 0.39 mm. for the control animals. After eight days' treatment with benzpyrene the tongues were 0.83 mm. and 0.80 mm. long; the tongues in the animals painted with benzene measured 0.88 mm. and those in the control mice 0.55 mm. After eleven days the corresponding figures were 1.12 mm. and 1.19 mm. in the benzpyrene, 1.25 mm. in the benzene and 0.85 mm. in the control groups. After fourteen days of application of benzpyrene, as also in the case of benzene, the wounds were closed, but in the untreated animal the tongue was still recognizable (tables 2 to 4, column 6).

Three and five days subsequent to operation there were four to six rows of epithelial cells at the insertion of the tongue in the benzpyrene-treated mice; this is not significantly different from the number found in the control group. One animal, in which only two to three rows of cells were present, had a marked inflammatory reaction around the wound. Between eight and eleven days after excision the epidermis in the benzpyrene-treated animals had reached its maximum thickness, seven to nine rows, compared with the maximum of four to five rows in the control series and of six to seven rows in the benzene group (tables 2 to 4, column 4). Subsequently the base of the tongue became thinner, and when the wound was closed the number of cell rows at the insertion of the tongue equaled that of the old epithelium.

Three and five days after operation the advancing tongue in the benzpyrene series was composed of two to four rows of greatly enlarged cells (table 4, column 5); after eight and eleven days the number of cell rows had increased to six or seven, which is higher than the maximum of four or five rows found in the benzene-treated and control mice (tables 2 to 4, column 5). Fourteen and twenty-one days after excision the former tongues were still recognizable as a thickened epithelial layer consisting of as many as eight rows of cells, which were, however, now less hypertrophic than at earlier stages. After twenty-eight days the recently regenerated could not be distinguished from the old epithelium. In the benzene-treated and control animals the corresponding condition had already been reached after fourteen and twenty-one days, respectively, when a return to the resting state had occurred.

The mitotic activity of the hypertrophic new epithelium in the benzpyrene series was great, although after three and five days of treatment the elevation of the mitotic count was only about the same as that in the benzene-treated mice (tables 3 and 4, column 8). After eight to fourteen days of painting with benzpyrene the mitotic count had risen to ten times the normal, which was the highest point reached, whereas in the benzene-treated animals it was elevated only five times. After

eleven and fourteen days the mitotic count in the former still remained at its peak, as did that of the control mice; in the benzene-treated group, on the other hand, the count at this stage had dropped to normal (tables 2 to 4, column 8). Even twenty-one and twenty-eight days after the excision the mitotic index in the benzpyrene-treated animals was still five to seven and one-half times higher than ordinarily, whereas in the untreated mice the mitoses had fallen to the normal level.

#### COMMENT

Benzene applied to regenerating epidermis of mice accelerated wound healing. The diameter of the wound decreased more rapidly under the influence of benzene than it did in control mice; in benzene-treated animals the mitotic index of the old as well as of the new epithelium was increased over that found for control animals; the epithelial tongues were slightly thicker and increased more quickly in length in the former than in the latter. Thus the migration of cells into the defect was hastened along with the intensification of proliferation.

The rapid drop of the mitotic count seen in the later stages in the benzene-treated animals is in agreement with the fact established by Loeb<sup>3</sup> that mitotic proliferation recedes promptly as soon as the defect has become epithelized. This stage of repair is reached more quickly in wounds that are under the influence of benzene than in those that heal spontaneously.

The acceleration of wound repair is probably due to the direct stimulation to proliferation of the marginal epithelium and perhaps also of the newly formed epithelium at the insertion of the tongue. Whether the migration of the cells is also directly stimulated by the benzene or whether it is secondary to the increased number of cells in the epithelial layer cannot be decided on the basis of the present experiments.

Benzpyrene applied to regenerating epithelium up to five days hastened wound healing and did so to about the same degree as benzene. This effect might, therefore, be attributable to the action of benzene alone. However, under its continued stimulation resulting from both the injury and the benzpyrene, the mitotic index in the epithelium rose to ten or more times the normal, whereas after application of benzene its highest average had been five and one-half to six and one-half times the normal. In the benzpyrene-treated animals the number of mitoses increased at first sharply in the marginal epithelium and more slowly in the new epithelium. This was followed by a period in which mitotic activity was greater in the new epithelium than in the old

3. Spain, K. C., and Loeb, L.: *J. Exper. Med.* 23:107, 1916.

epithelium; finally, a state was reached in which the mitotic count was the same in both the new and the old epithelium. This course of events resembles that seen during wound repair in control mice; it differs from it inasmuch as it takes place on a higher mitotic level. This increased mitotic proliferation also surpasses that observed in benzene-treated animals and must therefore be attributed to the action of the benzpyrene. If benzpyrene was applied for a period of four weeks after the making of the wound, it was still active when the stimulus to regeneration had ceased. This explains the failure of the mitotic count to return to normal as in control animals.

In spite of the increased epithelial proliferation, the complete closure of the wounds in the benzpyrene-treated animals lagged slightly behind that observed in the benzene-treated mice, although it was still hastened as compared with wound healing in control animals. From the second week on, the diameters of the wounds in the benzpyrene-treated mice were slightly larger and the advancing epithelial tongues were somewhat shorter than those in the corresponding benzene-treated mice.

Thus in the benzpyrene-treated animals the epithelization of the wounds was not hastened to the same extent as the proliferation of the cells. While cells were abundant, they failed to migrate into the defect at a rate commensurate with their increased multiplication.

A certain dissociation of cell migration from cell proliferation was found previously, when two or three months of treatment with benzpyrene had preceded the making of the wound.<sup>1</sup> In the present investigation there was an indication of a slight inhibition of cell migration when the carcinogen had been applied directly to the wound for eight days. This time difference may perhaps be explained by a different mode of reaction to benzpyrene of resting epithelium, on the one hand, and of regenerating epithelium, on the other. Moreover, a possible effect of benzpyrene on the cutis or the subcutaneous tissue might be

expected to be more marked when the substance is applied to a wound than when it is painted on intact skin. Changes in the texture of the wound base, such as edema and disintegration of collagen,<sup>4</sup> could therefore manifest themselves at an earlier experimental stage.

The nature of the injurious effect of benzpyrene is uncertain. The changes in the base of the wound might interfere with the stereotropic movement of the epithelial cells. On the other hand, the keratinization, which is more marked in the benzpyrene-treated animals than in any other group, might decrease the motility of the cells; or the inelastic keratinized epithelium might exert a mechanical centrifugal pull on the migrating epithelium and thus impede its movement toward the center of the defect. It is possible, furthermore, that cell proliferation, if stimulated beyond a certain optimum, interferes with the ameboid cell movement.

Investigations are in progress to clarify the discrepancy between the growth-promoting action of benzpyrene, on the one hand, and the comparatively delayed cell migration, on the other. In particular it is to be determined whether the latter is due to a direct effect of the benzpyrene or whether it is a secondary phenomenon.

#### SUMMARY

Benzene applied to regenerating epidermis of mice hastens wound healing by intensifying epithelial proliferation and by accelerating the rate of cell migration into the defect. Benzpyrene dissolved in benzene stimulates epithelial proliferation so that the proliferation is more marked than under the influence of benzene alone. Cell migration into the wound is accelerated; however, this acceleration is not commensurate with the increased proliferation of the cells. Thus, epithelization of wounds treated with benzpyrene is hastened as compared with the normal but is slower than after application of benzene.

4. Orr, J. W.: *J. Path. & Bact.* **46**:495, 1938.

## Case Reports

### BILATERAL METANEPHRIC AGENESIS WITH OTHER ANOMALIES

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Bilateral agenesis of the metanephros is of such infrequent occurrence as to warrant a review of its incidence. One hundred and thirty-five cases of bilateral renal agenesis have been reported previously. Several reviews of the literature have been made,<sup>1</sup> the last in 1940. No additional reports of cases have been found in the available literature since that review. The condition is usually accompanied by other congenital anomalies<sup>2</sup> but may occur in the absence of further embryologic derangement.<sup>3</sup> The case to be described now is of particular interest because of the multiplicity of malformations.

#### REPORT OF A CASE

The infant in whom the anomaly occurred was a patient of Dr. P. T. Bacon, of Springfield, Vt., who attended the mother at the time of delivery and secured permission for the postmortem examination. The mother was a primipara. Her last previous menstrual period began May 29, 1943. The family history revealed that a maternal cousin was jaundiced at birth and that a paternal cousin was microcephalic. The pregnancy was uneventful except for slight nausea and emesis during the third month. There were no signs of toxicity. The placenta was normal in all respects. The patient made movements and attempts at respiration at the time of birth. A large amount of mucus was aspirated from the upper part of the pharynx and the nares. Cardiac action was present, but respiration did not occur. A tracheotomy was performed and artificial respiration was attempted, both by manual means and by a mechanical resuscitator. After one hour no heart sounds could be heard, and the infant was pronounced dead.

**Postmortem Examination.**—The body was that of an apparently well developed white newborn girl, 45 cm. (heel to crown) in length and weighing, it was estimated, 2,000 Gm. The teeth were absent. The pupils were round, regular and equal at 0.4 cm. There were marked cyanosis and moderate hypostasis. There was no jaundice, edema or rigor. A recent tracheotomy

incision, 1 cm. in length, was seen immediately below the cricoid cartilage. There was a 2 cm. stump of moist umbilical cord attached firmly. The right foot was everted in a state of dorsal flexion. There was no anus, and normal-appearing skin covered the region immediately posterior to the introitus. Externally the introitus appeared normal. The breasts appeared normal.

An incision made through a panniculus adiposus 2 mm. thick revealed a smooth and glistening peritoneum. The diaphragm arched to the fourth rib on the right and to the fourth interspace on the left. The pleurae were smooth and glistening. There was a scant amount of clear fluid in the pericardial cavity. The thoracic viscera were removed in one block and

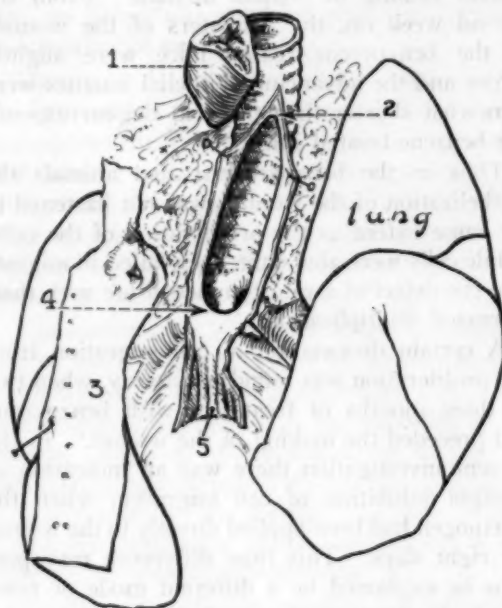


Fig. 1.—Dorsal aspect of the thoracic viscera: 1, proximal blind pouch of the esophagus; 2, cephalic end of the esophagotracheal fistula; 3, aorta; 4, caudal end of the esophagotracheal fistula at the bifurcation of the trachea; 5, caudal portion of the esophagus.

From the Department of Pathology, Dartmouth Medical School.

1. (a) Coen, E.: *Ann. univ. di med. e chir.* **267**: 52, 1884. (b) Rosenbaum, R.: *Frankfurt. Ztschr. f. Path.* **41**:136, 1931. (c) Madisson, H.: *Centralbl. f. allg. Path. u. path. Anat.* **60**:1, 1934. (d) Amolsch, A. L.: *J. Urol.* **38**:360, 1937. (e) Soloway, H. M.: *Ann. Surg.* **109**:267, 1939. (f) Hinman, F., Jr.: *Surg., Gynec. & Obst.* **71**:101, 1940.

2. Hinman.<sup>1f</sup> Soloway.<sup>1e</sup>

3. Grim, K. B.: *J. Urol.* **44**:397, 1940.

dissected from the dorsal aspect. The aorta appeared normal. The esophagus ended in a blind pouch at the level of the apexes of the lungs. Distally there was another portion of esophagus penetrating the hiatus of the diaphragm and entering the stomach. The proximal end of this portion became confluent with the trachea above and on being opened revealed a tracheal-esophageal fistula measuring 1.8 by 0.5 cm. This fistula terminated caudally at the bifurcation of the trachea (fig. 1). The bronchi appeared normal. The lungs were smooth and glistening, gray red, noncrepi-

tant and of increased density throughout. Section surfaces were dark red and exuded a red fluid. The heart appeared normal with a patent ductus arteriosus and a patent foramen ovale.

The liver externally was smooth, glistening and red-brown. The section surface was firm and red-brown. The gallbladder appeared normal. The spleen was smooth, glistening and dark gray-purple. Section surfaces showed a red-purple pulp with distinct lymphatic

structure ran from the introitus to the anterior portion of the uterus. This structure was lined with a smooth and glistening membrane. In the posterior aspect of this tube there was a blind pocket, 2 mm. in diameter and approximately 2 mm. deep, which protruded cephalad. The urachus joined the anterior surface of the uterus and was confluent with this tube. There was no bladder.

The lymph nodes appeared normal. The thymus was normal. The larynx was patent. The scalp was normal. The skull bones showed slight overlapping. The brain was not examined. The skeleton appeared normal.

*Microscopic Examination.*—The alveoli of the lungs were collapsed, and there was a large amount of hemorrhage throughout the interstitial spaces.

The uterus showed an acute inflammatory exudate in the perivascular spaces of the subserosa and occasional polymorphonuclear neutrophil leukocytes in the mucosa.

In the liver there was a moderate number of hemopoietic foci.

The following tissues were normal: adrenal glands, spleen, thymus, pancreas, heart, esophagus and aorta. The cloaca showed two muscular layers surrounding a tube lined with stratified squamous epithelium.

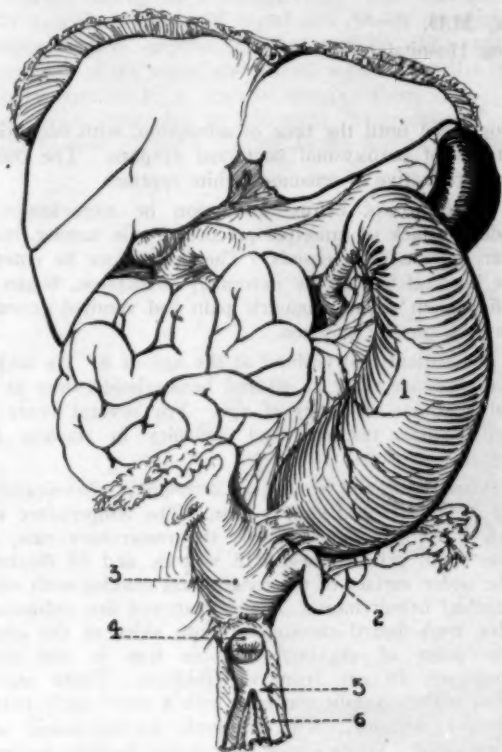


Fig. 2.—Ventral aspect of the abdominal viscera: 1, blind pouch of the sigmoid colon distended with meconium; 2, peritoneal adhesion between the sigmoid colon and the uterus; 3, bicornuate uterus; 4, cervix; 5, blind pocket of the hindgut; 6, cloaca.

markings. Externally the stomach and the small intestine appeared normal. The appendix lay free over the pelvic brim. The descending and the sigmoid colon were distended and presented a smooth, glistening, dark green, shiny peritoneal surface. The sigmoid colon ended in a blind pouch, which was adherent to the fundus of the uterus by thin, transparent peritoneal adhesions (fig. 2). The pancreas appeared normal. The adrenal glands were gray-yellow-brown, slightly lobulated, oval and flat, measuring 4 by 2 cm. The kidneys and ureters were absent bilaterally (fig. 3).

The uterus was bicornuate, the right side being larger than the left. The total structure measured 2.5 by 1.5 by 1 cm. (fig. 2). The fallopian tubes and the ovaries appeared normal. The epoophoron and the paroophoron could not be detected on either side. The external os of the cervix was lodged in a recess, 4 mm. wide, which was filled with clear mucoid material. What appeared to be a vagina and was a tubular

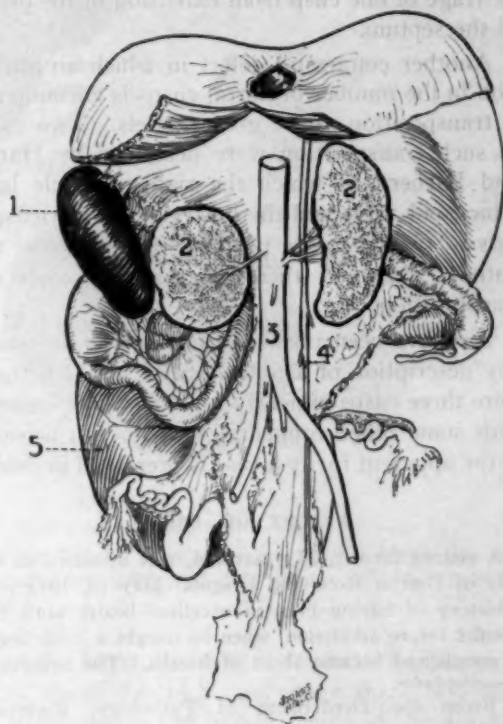


Fig. 3.—Dorsal aspect of the abdominal viscera: 1, spleen; 2, adrenal glands; 3, aorta; 4, inferior vena cava; 5, sigmoid colon.

#### SUMMARY

Bilateral renal agenesis was observed associated with other congenital defects of unrelated systems.

## TRICUSPID MITRAL VALVE

### A Report of a Case, with a Suggestion as to the Mode of Development

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DETROIT

Slight irregularities of the margin of the mitral valve are frequently present in normal hearts. Consistent slight irregularities have at times been alluded to as small cusps<sup>1</sup> and are found at the junction of the larger leaflets.

An alteration in the number of mitral leaflets occurs most frequently in relation to congenital defects of the interventricular septum. However, in septal defects the tricuspid valve is more often involved than the mitral.<sup>2</sup> The valve associated with this sort of abnormality usually exhibits cleavage of one cusp from extension of the defect of the septum.

Another congenital defect in which an alteration in the number of mitral cusps is encountered is transposition of the great vessels. Two cases of such transposition were described by Harris and Farber<sup>3</sup> in which the right ventricle bore a bicuspid valve and the left ventricle a tricuspid valve. Owing to the position of the vessels, the authors classified them as cases of corrected transposition.

We have been unable to find in the literature any description of a mitral valve in which there were three cusps of nearly equal size unassociated with some other congenital defect. On account of the apparent rarity a case is presented in detail.

#### REPORT OF CASE

A retired farmer, 77 years old, was admitted to the City of Detroit Receiving Hospital May 18, 1943 with a history of having been in excellent health until five months before admission, when he caught a cold, began to cough and became short of breath. The symptoms

From the Department of Pathology, Receiving Hospital.

1. Gray, H.: *Anatomy of the Human Body*, edited by W. H. Lewis, Philadelphia, Lea & Febiger, 1936, p. 531.

2. Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1924, vol. 2, p. 151.

3. Harris, J. S., and Farber, S.: *Arch. Path.* **28**:494, 1939.

progressed until the time of admission, with occasional attacks of paroxysmal nocturnal dyspnea. The cough was productive of tenacious white sputum.

Three weeks before admission he experienced a sudden attack of knifelike precordial pain lasting, however, only a few seconds. The day before he entered the hospital he became extremely orthopneic, began to suffer from vague epigastric pain and vomited greenish material on one occasion.

The patient had typhoid at the age of 8. He underwent appendectomy at 40 and hemorrhoidectomy at 45 and again at 60 years of age. For several years he had dysuria, nocturia and difficulty in starting the stream.

When examined he was an orthopneic, chronically ill but well developed elderly man. The temperature was 98.6 F.; the pulse rate, 76; the respiratory rate, 34. The blood pressure was 115 systolic and 85 diastolic. The under surface of the tongue was studded with small petechial hemorrhages. A few scattered fine pulmonary rales were heard throughout both sides of the chest. The point of maximal impulse was in the sixth interspace, 14 cm. from the midline. There was a harsh mitral systolic murmur with a short early mitral diastolic murmur. The pulmonic second sound was accentuated. There was a faint aortic diastolic murmur in the fourth interspace at the left sternal border. The heart was fibrillating rapidly with an apical rate of 160 and a peripheral rate of 76. The liver was at the costal margin. Rectal examination revealed prolapsed combined hemorrhoids and an enlarged, firm, nodular prostate. There was severe arteriosclerosis of the extremities.

The clinical impression was as follows: The patient had had slight mitral valvulitis for years. Superimposed on this, he probably had atherosclerotic changes in the valves, resulting in organic mitral insufficiency with slight stenosis. Complicating this old rheumatic heart disease, it was believed there was arteriosclerotic heart disease with left ventricular failure.

Laboratory reports indicated essentially normal conditions except for a blood urea nitrogen value of 76 mg. per hundred cubic centimeters. The Kline and Kahn tests were negative.

The electrocardiograms revealed auricular fibrillation, low voltage and the effect of digitalis. These changes were compatible with a nonspecific type of myocardial damage.

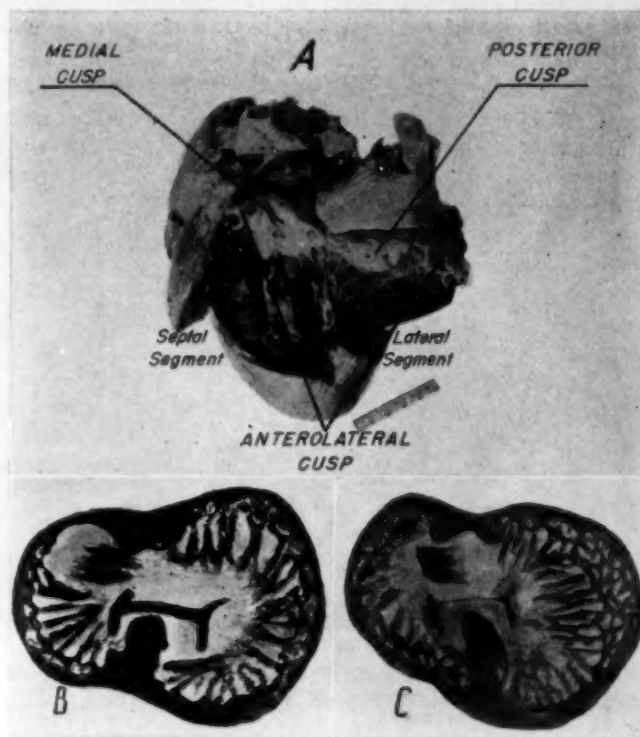
Therapy consisted of the administration of lanatosid C, theophylline ethylenediamine, ammonium chloride, oxygen, caffeine, sodium benzoate and sedatives.

Three days after admission he suddenly became cyanotic, his respirations became labored and he died about ten minutes after the onset of the cyanosis.

At autopsy the principal abnormalities were in the heart. The organ was greatly enlarged and weighed 660 Gm. When it was opened, the mitral valve exhibited three definite cusps (*A* in the figure). These were nearly equal in size and measured 5 cm. across the base. The width from summit to base was 2 cm. The septal portion of the left atrioventricular orifice was occupied chiefly by a medial cusp. This was adjacent to a posterior cusp of equal size which occupied the posterolateral portion of the orifice. The anterior portions of the septal and lateral segments of the orifice were covered by a slightly broader third cusp. This we have designated by the term "anterolateral," after Harris and Farber.<sup>3</sup> Owing to the line of section, the

ascites and pronounced passive congestion of the lungs, liver and spleen.

The excellent definition of the separate cusps and the approximate equality of size leave little doubt as to the character of the malformation. It is a tricuspid mitral valve. This anomaly may safely be assumed to be congenital in origin since the only pathologic alterations encountered in the heart were hypertrophy, diffuse myocardial fibrosis and mild sclerosis of the coronary arteries. The foregoing assumption is supported by the fact that an explanation can be readily made on the basis of established embryologic knowledge. Kramer<sup>4</sup> in his study of the partitioning



*A*, dissection of the left side of the heart showing the three cusps of the mitral valve.

*B* and *C*, drawing of the ventral view of two embryonic hearts illustrating the progressive fusion of the atrioventricular cushions and the notching of the mitral valve: *B*, from a 13 mm. embryo; *C*, from a 14.5 mm. embryo. (After Kramer.<sup>4</sup>)

septal portion appears on the left and the lateral portion on the right of the figure. The anterior papillary muscle gave chordae tendineae to the medial cusp. The posterior muscle gave chordae chiefly to the posterior and anterolateral cusps but also gave a few to the posterior margin of the medial cusp. The tricuspid and all remaining valves were free from any pathologic alteration. There was no septal defect, transposition of vessels or other congenital abnormality. The enlargement of the heart was due chiefly to hypertrophy of the left ventricle as judged from the measurements of the thickness of the right and left ventricular walls, which were 0.5 and 2.5 cm., respectively. Associated conditions were unilateral hydrothorax, moderate

of the heart observed that in the human embryo at about the 14.5 mm. stage there is a groove which marks the line of fusion of the dorsal and ventral atrioventricular cushions. Normally the groove disappears entirely, but for a time in either end there is a notch which is seen on the mesial border of each atrioventricular canal (*C* of the figure). Should the fusion be incomplete at the end of the groove in the left atrioventricular canal, the anterior cusp of the mitral value would

4. Kramer, T. C.: *Am. J. Anat.* 71:343, 1942.

be notched (normally the anterior cusp is formed from the union of the anterior and posterior endocardial cushions<sup>6</sup>). As the fusion in this position becomes more incomplete a series of malformations becomes theoretically possible, starting with a deeply notched anterior mitral cusp, through a completely bicuspid anterior leaflet to a

septal defect including the mitral valve. It therefore appears possible that the anterolateral and medial cusps of this heart represent an incompletely fused anterior mitral cusp and that the posterior cusp, which is normally the smaller, represents the true posterior mitral leaflet.

#### SUMMARY

A tricuspid mitral valve unassociated with any other congenital defects was observed in a farmer 77 years old.

5. Jordan, H. E., and Kindred, J. E.: Textbook of Embryology, New York, D. Appleton-Century Company, Inc., 1937, p. 138.

## CONGENITALLY INSUFFICIENT TRICUSPID VALVE ACCOMPANIED BY AN ANOMALOUS SEPTUM IN THE RIGHT ATRIUM

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Insufficiency of the tricuspid valve due to primary malformation of the valve is a rare condition. It was encountered in the heart which is discussed in this report. Maude Abbott<sup>1</sup> in 1908 stated that true congenital tricuspid insufficiency is rare, probably not a dozen cases being recorded at that time (including those in which it was due to fetal endocarditis). Herxheimer<sup>2</sup> in 1910 briefly reviewed the reported cases of congenital anomalies of the tricuspid valve as well as the cases of fetal

examples of Chiari's network and 3 examples of replacement of the eustachian and thebesian valves by larger septums, similar to the one described here.

### REPORT OF A CASE

A Negro girl, born normally at full term, died after five minutes, apparently of myocardial failure. An autopsy was made two and one-half hours after death. The body weighed 2,750 Gm. and measured 45 cm. from heel to crown. Externally the only abnormality noted was an extreme degree of cyanosis of the mucous



Fig. 1.—Drawing of the heart showing a view of the right atrium with its anomalous septum and the malformed tricuspid valve. I.V.C., inferior vena cava; C.S., coronary sinus; F.O., foramen ovale.

endocarditis leading to atresia of the right atrio-ventricular ostium.

The heart described in the present report also showed a large anomalous septum in the right atrium, a not uncommon anomaly. Yater<sup>3</sup> presented 11 examples of anomalous venous valve in the right atrium which he encountered in examining 120 hearts. Included were 4 typical

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1. Abbott, M. E., in Osler, W., and McCrae, T.: *Modern Medicine*, Philadelphia, Lea & Febiger, 1908, vol. 4, chap. 9, p. 323.

2. Herxheimer, G., in Schwalbe, E.: *Die Morphologie der Missbildungen des Menschen und der Tiere*, Jena, Gustav Fischer, 1909-1913, pt. 3, chap. 4, p. 474.

3. Yater, W. M.: *Arch. Path.* 7:418, 1929.

membranes and the nail beds. Each pleural cavity contained about 75 cc. of clear yellow fluid. The peritoneal cavity contained approximately 100 cc. of similar fluid.

When the thorax was opened, the dilated heart was seen to occupy almost all of the transverse diameter of the chest; this diameter was 10 cm., and the transverse diameter of the heart was 8.5 cm. The tremendously dilated right ventricle and atrium formed the greater portion of the cardiac mass; the left side of the heart was contracted. In situ the right atrium measured 5.5 by 4.5 by 4 cm., the right ventricle 5 by 5 by 4.5 cm., and the left ventricle 4 by 2.5 by 2.5 cm. The heart weighed 40 Gm., more than twice the average weight at term (17 Gm.). The left ventricle was hypertrophied, but otherwise the left side of the heart was not remarkable. The dilated right atrium and right ventricle also were hypertrophied. The foramen ovale and the ductus arteriosus were patent. There were no septal defects. The pulmonic, aortic and mitral

valves were normal. There were no abnormalities of the large vessels.

The tricuspid valve (fig. 1) was abnormal in regard to the number of cusps, their size, their gross structure and their attachment to the papillary muscles. There were only two cusps. The distance from the free edge of this valve to its point of attachment at the valve ring was greatly increased, measuring 1.8 cm., in contrast to that of the mitral valve, which measured 0.9 cm. In contrast to the normal smooth and homogeneous appearance of the mitral cusps, the cusps of the tricuspid valve consisted of narrow bands, alternately dense and semitransparent, running in the vertical axis. In addition, all along the auricular surface of the free edge of each cusp were numerous soft warty nodules, about 1 to 2 mm. in diameter and of the same color as the remainder of the valve. Finally, there were practically no chordae tendineae; the cusps were attached to the short, poorly developed papillary muscles and to the ventricular myocardium by a few tiny short strings. Consequently, the cusps were held closely against the myocardium, and although longer than

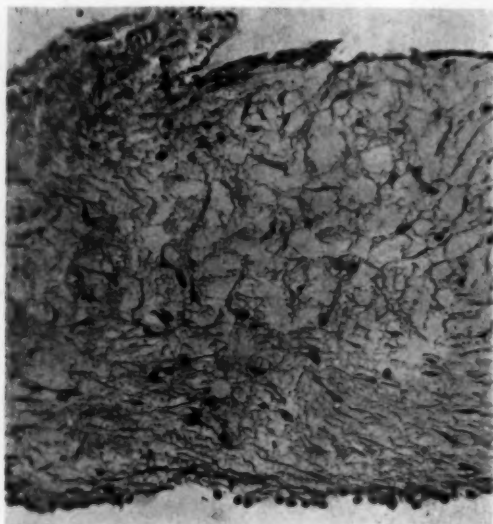


Fig. 2.—Microscopic appearance of one of the endocardial nodules of the tricuspid valve stained with hematoxylin and eosin.

normal in the vertical axis, were made insufficient by this abnormal attachment.

When examined microscopically the endocardial nodules appeared to be merely local enlargements of the valvular substance (fig. 2). They consisted of a loose cellular connective tissue formed of numerous diffusely scattered large fibroblasts with many fibrillar processes which served to make a fine fibrillary meshwork; they thus appeared to be composed of an immature type of connective tissue. These nodes were covered with a single layer of endothelial cells continuous with those over the remainder of the valve. There was no evidence of inflammation.

Situated in the right half of the right atrium was a large membranous septum, 3 by 2 cm. It was thin, smooth, and uniform in structure. Except for a few fenestrations at the edges it was a solid sheet of tissue. Its attachment was both by continuity of the membrane with adjacent structures and by intervention of thin fibrous bands. It was attached superiorly to the crista

terminalis and inferiorly to the endocardium of the valve ring just above the posterior cusp of the tricuspid valve. As indicated in figure 1, the membrane extended over the orifices of the coronary sinus and the inferior vena cava as well as over half of the foramen ovale. Microscopically, the membrane was found to be composed largely of dense connective tissue. Running through the center of the membrane in both vertical and horizontal axes were bundles of elastic tissue and cardiac muscle of varying thickness. Each surface was covered by a single layer of endothelial cells. There was no evidence of inflammation.

The following measurements were taken after fixation of the heart in Kaiserling's fluid, in the course of which the heart had become somewhat shrunken. The circumferences of the valves were as follows: mitral, 3.3 cm.; tricuspid, 5.5 cm.; aortic, 1.4 cm.; pulmonic, 1.3 cm. The thickness of the wall of the left ventricle was 5 to 6 mm. and that of the wall of the right ventricle 4 to 5 mm. The thickness of the wall of the left atrium was less than 1 mm. and that of the wall of the right atrium 2 to 3 mm. Both ventricles measured 3.1 cm. from base to apex. The greatest circumference of the left atrium in the transverse axis was 3.8 cm. and that of the right atrium 7.8 cm.

#### COMMENT

##### *Congenitally Insufficient Tricuspid Valve.*—

Congenital tricuspid insufficiency is a rare condition which may be caused by anomalies of the valve or of its attachments, by deformity resulting from maldevelopment of neighboring structures or by fetal endocarditis. The cases reported prior to 1910 were briefly reviewed by Herxheimer.<sup>2</sup> In the bibliography<sup>4</sup> of the 1,000 cases of congenital cardiac disease analyzed in Maude Abbott's *Atlas of Congenital Cardiac Disease*<sup>5</sup> there were titles relating to 41 cases of insufficiency or defects of the tricuspid valve. Of these cases, 36 were instances of such insufficiency complicating more important major cardiac defects; only 5 cases were listed in which the valvular condition represented the primary lesion of the heart. Of these 5 cases, 3 were apparently examples of Ebstein's disease<sup>6</sup>; the other 2 were cases of hypoplasia or aplasia of the tricuspid valve.<sup>7</sup>

Yater and Shapiro<sup>8</sup> presented the sixteenth case of Ebstein's disease in 1937 and reviewed the other authentic cases. In this disease the essential abnormality is a downward displacement of the tricuspid valve.

Ariel<sup>9</sup> presented a case of congenital mitral and tricuspid insufficiency occurring in a cyanotic

4. Bauer, D. deF., and Astbury, E. C.: *Am. Heart J.* **27**:688, 1944.

5. Abbott, M. E.: *Atlas of Congenital Cardiac Disease*, New York, American Heart Association, 1936.

6. Geipel, P.: *Virchows Arch. f. path. Anat.* **171**: 298, 1903.

7. Hotz, A.: *Jahrb. f. Kinderh.* **102**:1, 1923.

8. Yater, W. M., and Shapiro, M. J.: *Ann. Int. Med.* **11**:1043, 1937.

9. Ariel, M. B.: *Virchows Arch. f. path. Anat.* **277**:501, 1930.

male infant who died after two days. The atrio-ventricular valves consisted of large tumor-like structures, which he considered to be congenital overgrowths of the embryonic connective tissue of the endocardial cushions. Microscopically, these growths consisted of avascular collagenous tissue.

An example of congenital tricuspid insufficiency produced by anomalous attachment of the valve is given in Cabot case 25321.<sup>10</sup> The patient was a 7 month old boy who had a defect in the interventricular septum. One of the leaflets of the tricuspid valve passed through the septal defect and was anchored in the left ventricle instead of the right. This pulled one leaflet tightly against the right ventricular wall, appar-

growths extended along the free borders of all the cusps of the tricuspid and pulmonic valves. Microscopic examination of these nodules showed them to be covered with a single layer of endothelial cells and to consist of an abundant fibrillary matrix continuous with the endocardium; there were no signs of inflammation. An examination of the drawing of the heart indicates that the septal cusp of the tricuspid valve possessed a trabeculated structure similar to that in our own case.

The heart described in the case reported here showed abnormal development of the tricuspid valve together with hypoplasia of the papillary muscles and aplasia of the chordae tendineae. We are unable to suggest a more satisfactory

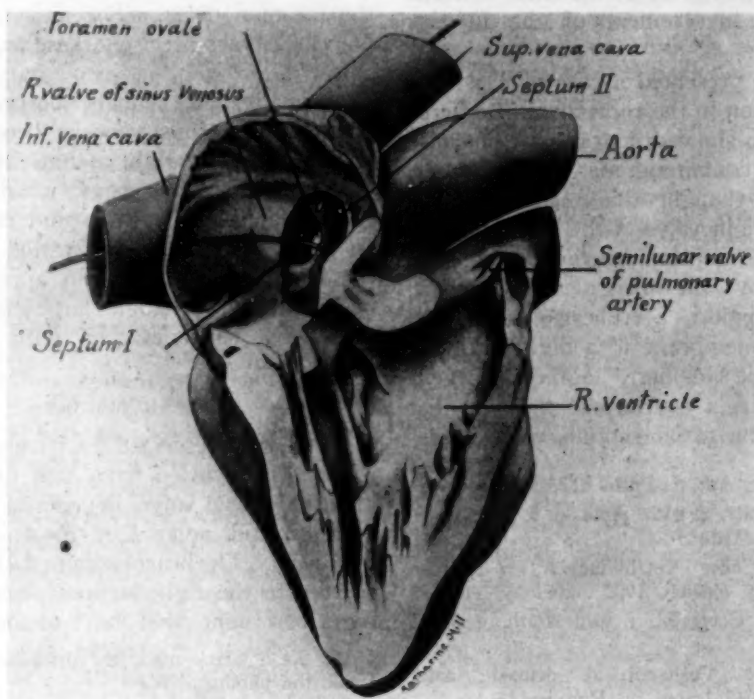


Fig. 3.—Heart of a 65 mm. human embryo showing a view of the right side (copied from Prentiss<sup>18</sup>).

ently producing insufficiency of the tricuspid valve.

The case reported here is quite similar to that of Graham Ross presented in Abbott's Atlas of Congenital Cardiac Disease.<sup>11</sup> That case is classified as one of congenital tricuspid insufficiency due to incomplete differentiation of the septal cusp. The heart was from a cyanotic boy aged 7 days. The marginal and infundibular segments of the tricuspid valve were well formed, but the septal cusp was adherent to the adjacent myocardium without the intervention of chordae tendineae. A mass of papillary endocardial out-

growth of the formation of these peculiar trabeculated cusps than the usually presented one which presumes an incomplete differentiation of the cusps from the endocardial cushions. The endocardial nodules most likely represent simple focal hyperplastic malformation of the endocardial cushions; there was nothing to suggest fetal endocarditis.

#### *Anomalous Septum in the Right Atrium.*—

Yater<sup>3</sup> presented a comprehensive review of the literature dealing with anomalies of the venous valves in the right atrium of the human heart. He found 22 typical examples of Chiari's network described in the literature and added a report of 4 of his own; the incidence in his series

10. Cabot Case 25321, New England J. Med. **221**: 239, 1939.

11. Abbott,<sup>8</sup> pp. 24 and 25, fig. 5.

of 120 hearts was 3.3 per cent. Helwig<sup>12</sup> reported 8 cases, an incidence of 1.5 per cent in routine autopsies.

Yater reviewed the interpretations of these anomalies of the valves and noted two main conceptions. Chiari's conclusion<sup>13</sup> was that the network is a remnant of the right valve of the sinus venosus and of the septum spurium. Looser<sup>14</sup> expressed the opinion that it is formed entirely by the right valve of the sinus venosus and a dislocation of fibers from their normal site by irregularities in the growth of the endocardium. Yater considered Looser's explanation as being nearer the truth and preferred to look on all folds or networks found in association with or replacing the eustachian and thebesian valves as remnants of the right valve of the sinus venosus with or without involvement of the inferior sinus septum.

Ruggieri<sup>15</sup> also presented a case of extensive membrane formation in the right atrium. Microscopic examination showed it to consist of dense connective tissue containing many thick elastic fibers. Ruggieri thought this membrane was formed from the right valve of the sinus venosus and also from the septum spurium, and cited cases reported by Sternberg and Gombert. According to Ruggieri, Sternberg<sup>16</sup> attributed the origin of the membrane to a division of the atrial septum, while Gombert,<sup>17</sup> agreeing in general with Sternberg's conclusion, thought that this division of the atrial septum was supple-

mented by an unusual growth of the valves of the sinus venosus. Ruggieri disagreed with the concept that the interatrial septum played a part in the formation of such a membrane.

It is our opinion that the anomalous septum in our case represents a persistent right valve of the sinus venosus. Its attachments and relationships are identical with those of the right valve of the sinus as seen in the heart of the 65 mm. embryo described by Prentiss<sup>18</sup> (compare figs. 1 and 3). In this fetal heart the right valve of the sinus venosus is attached superiorly to the crista terminalis and inferiorly to the valve ring; it occupies the right half of the right atrium and extends over the orifices of the coronary sinus and the inferior vena cava as well as a portion of the foramen ovale. The anomalous septum in our case shows precisely these anatomic relationships.

Normally, the cephalic portion of the right valve of the sinus venosus becomes the crista terminalis of the right atrium; the remainder is divided into two parts which become, respectively, the eustachian and thebesian valves. In the case under consideration the division of the right valve of the sinus apparently failed to occur, leaving a single large membrane which developed concomitantly with other cardiac structures.

#### SUMMARY

In the case described the tricuspid insufficiency apparently resulted from lack of differentiation of the tricuspid valve, hypoplasia of the papillary muscles and aplasia of most of the chordae tendineae. The heart contained a large anomalous septum in the right atrium, probably representing a persistent right valve of the sinus venosus.

Mr. Elon Clark made the drawing and Mr. Robert Little the photographs.

18. Prentiss, C. W.: *Text-Book of Embryology*, Philadelphia, W. B. Saunders Company, 1915, p. 261.

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14. Looser, E.: *Ueber Netzbildungen im Rechten Vorhofe des Herzens*, Zurich, 1902; cited by Yater.<sup>3</sup>
15. Ruggieri, A.: *Centralbl. f. allg. Path. u. path. Anat.* 63:129, 1935.
16. Sternberg, C.: *Verhandl. d. deutsch. path. Gesellsch.* 16:253, 1913; cited by Ruggieri.<sup>15</sup>
17. Gombert, H.: *Beitr. z. path. Anat. u. z. allg. Path.* 91:483, 1933; cited by Ruggieri.<sup>15</sup>

## Laboratory Methods and Technical Notes

### DEHYDRATION IN HISTOLOGIC EMBEDDING ELIMINATED BY THE USE OF A WATER-SOLUBLE SYNTHETIC PLASTIC

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In a preliminary note we<sup>1</sup> introduced the use of the synthetic resin polyvinyl alcohol as an embedding material.

The classic methods for preparing tissues for microscopic study have a number of disadvantages. Among these is the extensive dehydration through increasing concentrations of alcohol, followed by various hydrocarbons, such as ether, xylene and aniline. One cannot help feeling that such drastic measures must impair the fidelity of the final appearance of the microscopic tissues to their likeness in the living state. This observation is given added weight when one considers that the water content of plant and animal tissues is 70 to 95 per cent.

A second disadvantage of current technic is that one must set aside a separate block of tissue for fat stains, since the primary block has been incidentally defatted in the process of dehydration. Furthermore, one must go to the trouble of making frozen sections.

Further problems are encountered in certain special cases. Thus, in our laboratory, where we are concerned with the preparation of microscopic slides of the eye, as a unit, the great drawback is the marked shrinkage of the eye in the alcohols, and, in addition, the variation in the degrees of shrinkage of different coats, with consequent serious distortions. In the attempt to overcome this, an extremely long allowance of time is customary.

At this time, also, alcohol and xylene are becoming increasingly difficult to obtain.

In the search for a method which would avoid dehydration before embedding, we thought of using a water-dispersible plastic and came on the recently synthesized forms of the resin polyvinyl alcohol. These are more familiar to the trade as PVA. These substances are readily though limitedly soluble or dispersible in water. They can be made to form gels of a consistency varying with the concentration of plasticizer used.

We are presenting the histologic method which we have arrived at after a year and a half of experimentation—with the realization that further perfecting is necessary.

This work was done under a provision from the Aaron Garfunkel Fund, in the Ophthalmological Laboratory of the Montefiore Hospital, service of Dr. Robert K. Lambert.

1. Lubkin, V., and Carsten, M.: *Science* **95**:633, 1942.

#### TECHNIC

The powder (supplied to us by E. I. du Pont de Nemours) is the fully synthesized resin known as grade RH-393 PVA.

A solution containing 20 per cent by weight is prepared by suspending the powder in water at room temperature, breaking up the lumps, then stirring well while heating the solution in a steam bath to a temperature of 75 to 85 C. The heating is continued until the air bubbles have been removed from the viscous fluid. To the cooling solution is added 20 per cent of glycerin by weight.

Tissue fixed in a 4 per cent solution of formaldehyde, rinsed in water and of the dimensions ordinarily taken at autopsy is placed directly into the 20 per cent polyvinyl alcohol and glycerin solution in small covered dishes. The attainment of a hardness adequate for sectioning requires a variable time, averaging two weeks for the ordinary specimen. The process appears to be hastened somewhat by the use of a temperature of 56 C. for about an hour a day. During the hardening, as soon as the gel is sufficiently firm, it is turned out of the dish and trimmed into blocks covering all surfaces of the tissue by 3 to 5 mm. After much experimentation, the best material for affixing the block to wooden carrier-blocks was found to be the 20 per cent solution of polyvinyl alcohol and glycerin. This is poured over the surface of the wooden block, the embedded tissue is mounted and covered again by a thin layer of the same solution. This is allowed to dry for twenty-four hours before sectioning. Bausch and Lomb blocking pitch was also found useful for this purpose. The blocking pitch is a product put up in stick form, like sealing wax, and used commercially in the manufacture of lenses.

The routine of sectioning is that used for celloidin (a concentrated preparation of pyroxylin) except, of course, that the block is moistened with water rather than with alcohol. The sections may be cut as thin as 5 to 6 microns, occasionally 4 microns. They unroll in lukewarm water and are mounted immediately for staining. The film of polyvinyl alcohol remains undissolved on the slide and with stains is slightly acidophilic.

The stains are made as usual. Hematoxylin-eosin, Weigert-Van Gieson, Masson's trichrome, sudan IV and, on nerve tissue, Nissl and Spielmeier's myelin stains have been successfully applied.

Mounting is done in the conventional manner with balsam or clarite.

With respect to the preservation of the blocks, they are best kept (as we have some for eighteen months) in a moist atmosphere, such as that provided by a bottle from the cork of which is suspended a moist pledget. It is well, also, to add a small percentage of formaldehyde to stock solutions of polyvinyl alcohol and to the preserving jars to discourage the growth of fungi. Before this measure was adopted, fungi

occasionally grew on the surfaces of the blocks. They never infiltrated or impaired the embedding.

Polyvinyl alcohol-glycerin solution need not be made up freshly each time it is used. When the stock solutions harden, they may be melted in a water bath.

It is to be noted that the plastic is remarkably inexpensive and that the growing shortage of alcohols points up the need for a process which avoids their use.

Sections for fat stains are cut from the same block as all other sections.

in this way as against those placed directly into the 20 per cent solution of polyvinyl alcohol with glycerin. Hardening at different temperatures was then tried. There was no significant difference at 5 and at 37 C. Several blocks were allowed to harden to completion at room temperature; these, while they took somewhat longer, were histologically satisfactory. Various gelling agents were added in suitable concentrations; the results were in general unsatisfactory, with marked distortion of tissue. Those we tried were resorcinol, pyrogallol, borax, water glass and pectin.

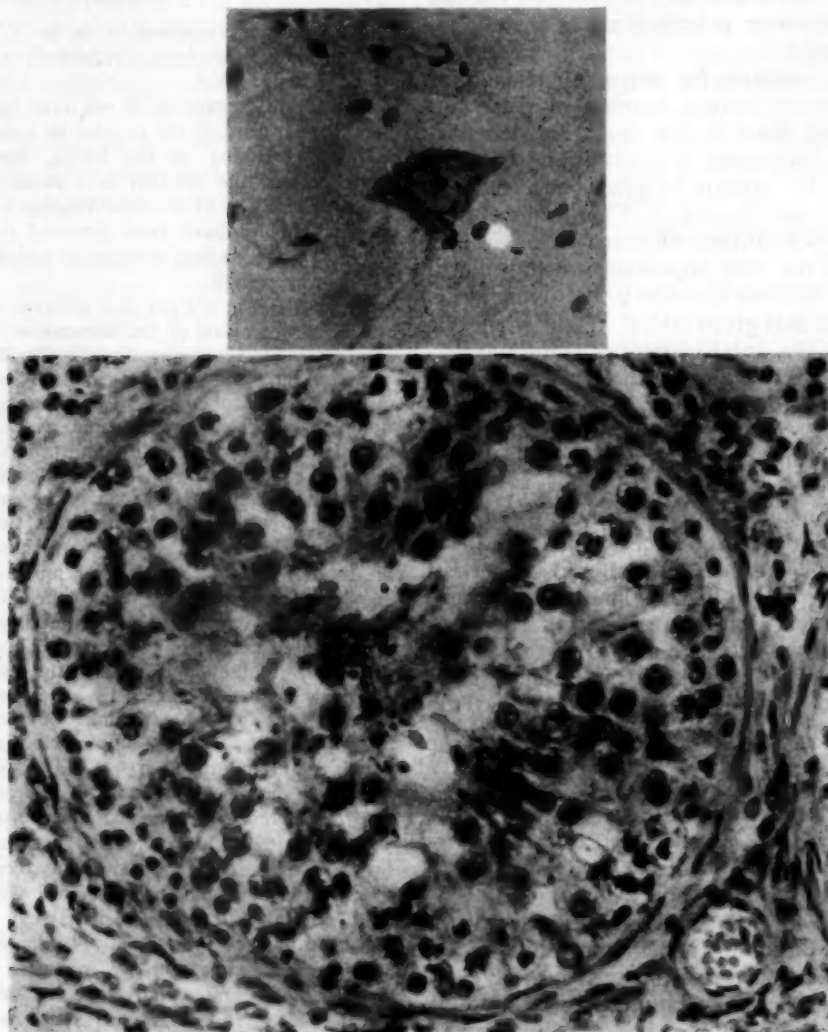


Fig. 1.—Upper: Anterior horn cell of a human spinal cord; Nissl stain;  $\times 600$ . Lower: Normal testis showing spermatogenesis; hematoxylin-eosin;  $\times 400$ .

#### EXPERIMENTAL STUDIES

We have experimented with almost every phase of the procedures outlined in an attempt to shorten the process and to perfect it in other ways. The chief problem was the slow pace of the hardening.

Numerous attempts at acceleration were carried out. At first it seemed advisable to pass the tissues through 5 per cent and 10 per cent solutions of polyvinyl alcohol with glycerin, as a preliminary maneuver, to facilitate penetration by the 20 per cent solution. However, we have noticed no difference in blocks prepared

The next problem to be attacked was that of shrinkage. Polyvinyl alcohol alone shrinks excessively and becomes too hard and glassy. For this reason the plasticizer is added routinely. The best results in this direction are obtained by adding small amounts of fresh polyvinyl alcohol-glycerin solution at intervals during the gelling process. Another attempt to eliminate shrinkage entirely consisted in a gradual substitution of glycerin in one series, and of ethylene glycol in another, for the water content of the tissues before embedding, by passing the tissues through increasing concentrations of these substances before dropping them

into the polyvinyl alcohol-glycerin solution. The intention was to prevent whatever degree of shrinkage was due to the evaporation of water by thus eliminating the water. No noteworthy improvement, however, resulted.

The stained sections were mounted in Canada balsam or, better, in clarite, with xylene, toluene or carbol-

oil immersion. For this purpose sections were mounted in glycerin gelatin and in polyvinyl alcohol itself. This was adequate for fat stains; from the point of view of clarity with higher magnifications, however, this method left something to be desired.

The preservation of the polyvinyl alcohol blocks in a moist atmosphere for any considerable time tended

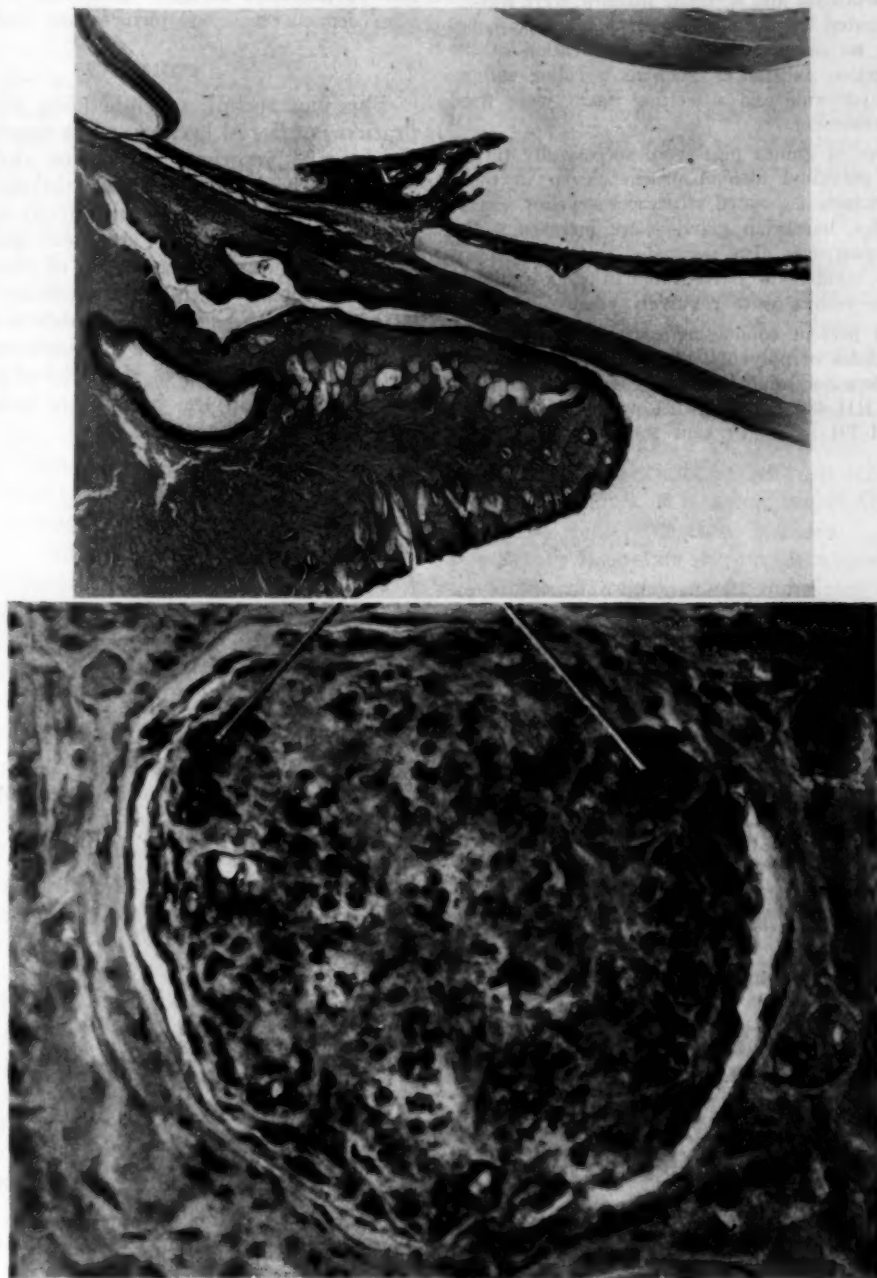


Fig. 2.—Upper: Structure of the angle of the anterior chamber in a guinea pig eye; hematoxylin-eosin;  $\times 28$ . Lower: Fatty degeneration in a renal glomerulus; sudan IV stain;  $\times 450$ . Angular lines indicate fat globules. This section was cut from the same block as those for routine stains.

xylene being used as clearing mediums with equal success. Attempts were made to avoid dehydration at this point by using water-soluble stains and by trying to find a water-soluble mounting medium with a high enough refractive index to permit adequate study by

to render them soft and swollen. However, they uniformly regained their former consistence after a short exposure to the air at room temperature. Unstained sections mounted on slides with egg albumin would likewise be kept in a moist chamber. Another way

of preserving unstained sections is to keep them in low concentrations of formaldehyde.

The entire gamut of tissues taken at autopsy was utilized during our experimentation. No difference in their reaction to the embedding medium was observed—with two exceptions: First, brain and cord were particularly satisfactory; second, highly fatty tissues like subcutaneous fat and acellular marrow were incompletely penetrated by the solution of polyvinyl alcohol and glycerin no matter what the concentration of the alcohol. Various substances, such as pyridine sulfate, ammonium hydroxide and a wetting agent were tried without improvement.

Halved eyes of guinea pigs were successfully turned out by the polyvinyl alcohol process, even in those instances in which associated structures—eyelids, extraocular muscles, harderian gland—were included. The lenses of human eyes also responded well. However, in a limited number of halved human eyes similarly embedded the results were relatively poor.

We are at present conducting experiments with the remaining grades of polyvinyl alcohol, as well as with other available water-soluble plastics. Grades RH-349 A, RH-391 A, RH-488 and RH-623 were tried without success. RH-391 in 20 per cent solution without gly-

cerin can be used as an embedding medium; however, the sections do not turn out as evenly as do those embedded in RH-393.

In photographing specimens it was noted that there is slight unevenness in the dispersion of light on the photographic plate in higher powers of magnification. This may be due to the refraction of light through the film of polyvinyl alcohol. However, as the illustrations demonstrate, good pictures are obtainable.

#### COMMENT

This new technic of embedding without dehydration is offered because of its timeliness in the face of the growing scarcity of alcohol and of the usual hydrocarbons. Furthermore, the opportunity to obtain fat stains from standard tissue blocks represents a step forward. Another point is that despite the length of time at present required for hardening, the number of manipulations to which the tissue is subjected is reduced to a minimum. Finally, the exploitation of the tremendous potential of the field of plastics may be accelerated in the interest of histologic progress.

## General Reviews

### IRRITATION AND CARCINOGENESIS

I. BERENBLUM, M.D., M.Sc.

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The old uncompromising belief that "chronic irritation is the cause of cancer" has as its counterpart the more recent but equally uncompromising attitude that "irritation has nothing whatever to do with cancer." Neither takes fully into account all that is known about the mechanism of carcinogenesis, and both suffer from oversimplification.

There is nowadays a growing tendency to ignore this issue of a possible relationship between irritation and carcinogenesis on the ground that the term "irritation" is too ambiguous. This seemingly plausible attitude constitutes in fact little more than an attempt to evade a difficult problem (though avoidance of ambiguity is admittedly an important preliminary to solution). After defining precisely what is meant by "irritation," or after substituting for it a more scientific term, the question still remains: Is this condition—whatever its name may be—associated with carcinogenesis or not?

#### THE NATURE OF IRRITATION

An irritant is a substance or an agency injurious to living tissue. The term "irritation" refers, therefore, to any harmful action on living cells. The result of this harmful action is partly passive (actual damage) and partly active (the response of the tissues to the damage).

The immediate response consists of that series of changes (hyperemia, increased permeability of the smaller blood vessels, exudation of fluid and mobilization of cells from the blood) which constitutes the process of acute inflammation. The late response consists of a proliferation of the affected cells (parenchymatous as well as interstitial). The immediate response is a pure defense measure; the late response represents a stage in the process of repair.

These two phases of response may vary greatly in relative intensity. After a single injury of sufficient severity, the acute inflammatory reaction is the predominant feature of the response, with hyperplasia appearing as a relatively inconspicuous process at the end.

From the Oxford University Research Centre of the British Empire Cancer Campaign, Sir William Dunn School of Pathology, Oxford University.

When there is chronic irritation, especially if the injury is mild but frequently repeated, evidence of the acute inflammatory phase may be slight or apparently absent, while the hyperplastic changes become cumulative and dominate the picture.

Considered from the point of view of a possible relation to carcinogenesis, irritation may be defined arbitrarily as "unphysiologic stimulation which, being potentially destructive, elicits a continued state of reparative hyperplasia." By this definition the problem is intentionally narrowed to conform to the prevailing belief that if there is an association between irritation and tumor formation, it is by virtue of the cell proliferation that irritation induces. It is thus possible to formulate the problem more precisely in terms of response, by inquiring what part reparative hyperplasia plays in the process of carcinogenesis.

This provides a double approach for the elucidation of the problem: (1) from the angle of the irritant and (2) from that of the result of the irritation. The first approach resolves itself into an inquiry as to whether all irritants are carcinogenic and whether all carcinogens are irritants. In the second approach one views the problem in a more fundamental form which calls for an understanding of the basic difference between hyperplasia and neoplasia and between preneoplastic hyperplasia and ordinary (reparative) hyperplasia, and thus one deals more intimately with the mechanism of carcinogenesis.

A comprehensive review of the literature covering this wide field is impossible in a short article. It is proposed, therefore, to deal rather briefly with those aspects that are already well established and to devote more attention to controversial issues and to animal experiments specially designed to elucidate the problem under review.

#### ARE ALL IRRITANTS POTENTIALLY CARCINOGENIC?

This question presents the problem in its crudest form: An answer in the affirmative would mean that irritation plays an essential part in the production of tumors, though how or why

reparative hyperplasia becomes converted into neoplasia would still remain obscure. An answer in the negative would mean that irritation is not by itself responsible for the production of tumors, though it might still conceivably play a vital part in carcinogenesis. Thus in either event the answer to this question can serve only as the starting point for further investigation of the major problem.

With the physical agents designated by the term "radiation" there is an apparent correlation between the power of producing injury of tissue and the ability to induce tumors. Thus, roentgen rays, gamma rays and ultraviolet rays are all carcinogenic, while cosmic rays, visible light and the waves used in wireless transmission (hertzian waves), are not. But here the analogy ceases, for with most other types of irritation, whether physical (mechanical, thermal and other agents), parasitic (viruses, bacteria or higher forms of organisms) or chemical, no such correlation can be found.<sup>1</sup>

Many chemical irritants have been tested for carcinogenic action experimentally, and many others have been studied from reliable clinical evidence. Only a small proportion have been found to possess carcinogenic action, and even with these it has not always been possible to deduce the potency of carcinogenic action from the irritative effects. These conclusions are clearcut and undisputed, but as regards other forms of irritants (e. g., mechanical or thermal) the published evidence is more conflicting and calls for a more detailed discussion.

To a certain extent the conflict arises from different notions as to the meaning of the term "trauma." Some use it to embrace all forms of irritation (physical, chemical, parasitic and other forms); some restrict its use to physical irritation (including mechanical and thermal influences and effects of various types of radiation); others confine its use to mechanical injuries only; while others restrict its use still further, distinguishing between severe mechanical injury (true trauma) and repeated mild mechanical injuries (friction). When the term is used sometimes in one sense and sometimes in another by the same author,<sup>2</sup> confusion becomes extreme.

In this review the term "trauma" will refer to one or a few single mechanical injuries of sufficient severity to elicit demonstrable evidence of gross damage of tissue; the term "friction"

will refer to a succession of frequently repeated mild mechanical injuries, the damage produced by each injury being negligible but the cumulative effect being sufficiently pronounced to produce well marked reparative hyperplasia.

The idea that trauma may be responsible for the development of a tumor is widely held both by the general public and by members of the medical profession. Published opinion on the subject has ranged from the statement that 44.7 per cent of all malignant tumors are due to trauma,<sup>3</sup> to the view that there is no proof that any tumor has ever been caused by trauma.<sup>4</sup> This striking divergence of opinion is partly illusory, reflecting differences of thought as to the meaning of "trauma," but it partly represents a true difference in the interpretation of the facts.

It is a common fallacy in logic to assume that because injury normally leads to a swelling, the appearance of a mysterious swelling must be due to a preceding injury, and the tendency to rationalize the presence of a swelling by imagining an association with injury is great. Many authors have expressed the belief that the question of compensation may serve consciously or unconsciously as an added factor in this process of rationalization.<sup>5</sup>

Thiem,<sup>6</sup> Knox,<sup>4</sup> Ewing<sup>7</sup> and others who have made a special study of the problem have laid down some rigid conditions or postulates that must be fulfilled before the alleged association in any particular case can be accepted as scientifically proved. These include: (1) demonstrable evidence of injury (e. g., a wound, a hematoma, a scar, a fracture); (2) identity of the injured area with the site of the tumor; (3) histologic proof that the lesion is neoplastic and that it is of a kind compatible with the affected tissue (the latter, to differentiate it from a metastasis, localized by the injury); (4) convincing evidence of previous integrity of the wounded part (to exclude the possibility that the injury had merely drawn attention to a preexisting tumor at that site); (5) a reasonable time relation between the occurrence of the injury and the development of the tumor (what constitutes a reasonable time relation is difficult to define, but it is generally agreed that a few weeks is too short); (6) the absence of a known carcinogenic environment which would itself be sufficient to account for the tumor.

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5. Moritz, A. R.: The Pathology of Trauma, London, Henry Kimpton, 1942.

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1. Leitch, A.: Compt. rend. Cong. du cancer **2**:39, 1923. Woglom, W. H.: Arch. Path. **2**:533 and 709, 1926.

2. Behan, R. J.: Relation of Trauma to New Growth, London, Baillière, Tindall & Cox, 1939.

Most of the thousands of recorded cases of "traumatic tumor" do not satisfy these requirements,<sup>8</sup> but a few do seem to conform, and it is about these that agreement is difficult to reach. Some authors are satisfied that the existence of cases which do conform constitutes convincing evidence that trauma is carcinogenic; others are convinced, however, that the proportion of cases that conform is so small in relation to the total number of injuries as to suggest a fortuitous association. The rarity of tumor at the site of an old wound among the thousands of casualties from the war of 1914-1918<sup>9</sup> supports the opinion of the skeptics. So does the fact that no one has ever succeeded in producing tumors in animals by traumatization alone.

Thus, in view of the extreme frequency of traumatization in man and the extreme rarity of tumors "proved" traumatic, trauma cannot be accepted as an important or frequent cause of cancer.

In judging the evidence of an alleged association between friction and tumor, the relevant criteria must be modified somewhat both in detail and in point of emphasis. There is seldom doubt about the occurrence of repeated irritation (as opposed to a single trauma), and the possibility of the tumor having preceded the injuries can usually be excluded as well. On the other hand, just because of the long duration of the injuries, it may be difficult to exclude with certainty that another carcinogenic factor has not been operating at the same time. Furthermore, though friction by definition implies a succession of mild injuries, it is by no means uncommon for the process to be complicated by one or more severe injuries, with resulting ulceration and infection. A clear decision about the part played by friction is therefore often difficult.

As examples of these complications, the following may be cited: carcinoma of the bridge of the nose attributed to irritation from ill fitting spectacles may in fact be due to sunlight; cutaneous tumors among workmen in engineering and related industries attributed to mechanical injuries may owe their origin to carcinogenic lubricating oils; carcinoma of the tongue, though often attributed to irritation from jagged teeth or an ill fitting denture, cannot be assigned with certainty to one single cause so long as other factors (e. g., excessive smoking, hot food or syphilitic infection) are suspected with as much or as little justification. In this connection one may note a recent report<sup>10</sup> of

carcinoma of the tongue in monkeys, among which none of the aforementioned factors was implicated. The frequent allegation that the recorded increase in the incidence of tumor of the lung in man is due to nonspecific irritation (from inhaled dusts or other substances) or to the resulting pneumonic or bronchitic inflammations receives little, if any, support either from statistical studies<sup>11</sup> or from general considerations.<sup>12</sup> The same observation applies to carcinoma of the stomach.<sup>13</sup>

Finally, there is no evidence that tumors are unduly prevalent at sites of uncomplicated manifestations of chronic mechanical irritation (e. g., corns or calluses), nor is it possible to induce tumors in animals by friction alone. Chronic mechanical irritation (friction) cannot, therefore, be accepted as a common or even a likely cause of tumor formation.

The relation of thermal injuries to carcinogenesis is complicated by the fact that they do not represent a single entity. Apart from difference in extremes of heat and cold and in severity of damage produced (burns and frost-bites), difference in method of induction is also an important factor (whether by naked flame, hot solids, hot liquids, hot vapors or gasses or electricity). From the point of view of carcinogenesis the deposition of soot (from a naked flame), the possibility of actual synthesis of a carcinogenic tar in the process of charring and secondary infections in healing wounds are hypothetical factors that must be taken into account.

On the other hand, the available evidence that thermal irritation can lead to the production of tumors is for many reasons more convincing than that concerning mechanical injuries: (1) Evidence of a previous burn is more often unmistakable; (2) the recorded incidence of tumors due to such injuries is higher than that of tumors due to mechanical injuries<sup>14</sup>; (3) when a burn and a subsequent tumor occur, as often happens, at a site where in general tumor is normally rare, the probability of a true association between the two is strengthened, and (4)

10. Steiner, P. E.; Klüver, H., and Brunschwig, A.: *Cancer Research* **2**:704, 1942.

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14. (a) Treves, N., and Pack, G. T.: *Surg., Gynec. & Obst.* **51**:749, 1930. (b) Schrek, R.: *Arch. Path.* **31**:434, 1941.

8. Knox.<sup>4</sup> Ewing.<sup>7</sup>

9. Wainwright, J. M.: *Am. J. Surg.* **5**:433, 1928.

experimental confirmation in animals<sup>15</sup> adds credence to clinical evidence which by itself might have been considered merely suggestive.

Accidental burns are common in man. Usually they heal satisfactorily, leaving a quiescent scar or, if superficial, no scar at all. On rare occasions, however, the site of a severe burn becomes the site of a tumor which develops either within a relatively short period (usually less than two years) in a persistent ulcer (known clinically as a Marjolin's ulcer) or at a much later period (e. g., some thirty years after the initial burn), long after the original lesion has healed, the scar ultimately breaking down and developing into squamous carcinoma. Both the "acute" and the "latent" type of burn tumor have been induced experimentally in animals,<sup>16</sup> but, as in man, the incidence is low as compared, for instance, with that of the tumor induced by tar.

Repeated freezing of the skin is also carcinogenic, as has been demonstrated experimentally in mice.<sup>16</sup> Though frostbites are much less common in man than burns, and tumors arising from them would therefore be expected to be rare indeed, several have in fact been reported in the literature.<sup>17</sup>

Finally, attention may be drawn to experiments specially designed to permit study of the relation between irritation and carcinogenesis. Mention has already been made of the numerous chemical and other irritants tested for carcinogenic action on animals, and of the fact that the results do not support the view that irritation per se is a deciding factor.<sup>1</sup> A more decisive approach would be to test the action of a severe irritant in different concentrations ranging from frankly necrotizing concentrations to those that are entirely without irritative effect. This has been done with mustard gas,<sup>18</sup> and no concentration was found to be truly carcinogenic, in spite of the fact that at some concentrations a degree of irritation (as judged by the amount of hyperplasia) was induced which corresponded closely to that obtained with a known carcinogenic tar. When the mustard gas and the tar were diluted so that the irritative effect of the two together was comparable to that of whole tar, repeated application of a mixture of the two failed to produce tumors. Finally, when dilute mustard gas was applied concurrently with whole tar, the carcinogenic action of the latter was not

augmented but, on the contrary, was inhibited to a marked degree.

Thus, to the question "Are all irritants potentially carcinogenic?" the answer is emphatically "No."

#### ARE ALL CARCINOGENIC AGENTS IRRITANTS?

This question appears to be more fundamental than the one heading the previous section, since a negative answer would seem to rule out the possibility that irritation plays an essential part in the process of carcinogenesis. Yet, even this requires qualification, depending on the definition of a carcinogenic agent. Is the term to include the viruses that produce tumor, and is it to include agents that become carcinogenic only after undergoing chemical change in the body?

With regard to tumor-producing viruses, it is clear that the mechanism involved in the neoplastic transformation is entirely different from that in the action of a carcinogen such as 3,4-benzpyrene. The virus acts specifically on one particular type of tissue in a particular species of animal, producing a particular kind of growth, whereas the carcinogen can act on a variety of different tissues in different species of animals, producing accordingly many different kinds of tumor. The virus directly converts a perfectly normal cell into a tumor cell. The carcinogen produces, in the first instance, a long-continued state of "preneoplastic hyperplasia"; in other words, the neoplastic transformation does not occur from the start. The virus persists and multiplies within the neoplastically altered cell, and as far as is known, this persistence is essential if the latter is to continue to behave in a neoplastic fashion, whereas the carcinogen does not persist indefinitely within the cell, nor is its action (or presence) required for the continuance of the neoplastic state.

It would be out of place here to enter into a discussion as to the significance of this fundamental difference between a virus and a true carcinogen. However, attention may be drawn to two opposite theories on the subject. The one presupposes that a tumor-producing virus exists in every tumor whether its presence can be technically demonstrated or not, and the other accepts the apparent absence of virus as evidence that none is present. According to the former theory, the postulated presence of a virus in every tumor induced by a carcinogen implies that the two processes represent two stages in the neoplastic transformation and are not two different examples of tumor-producing agents; according to the latter theory, the virus and the carcinogen are independent tumor-producing

15. Bang, F.: *Bull. du cancer* **14**:203, 1925.

16. Berenblum, I.: *Brit. J. Exper. Path.* **10**:179, 1929.

17. Haagenzen, C. D.: *Am. J. Cancer* **15**:641, 1931. Andrews, G. C., and McNitt, C. W.: *M. Clin. North America* **14**:1507, 1931. Schrek.<sup>14b</sup>

18. Berenblum, I.: (a) *J. Path. & Bact.* **32**:425, 1929; (b) **34**:731, 1931.

agents, involving separate and distinct mechanisms. Neither theory demands that a virus should be considered as a true carcinogen, and so the question of a tumor-producing virus being or not being an irritant is irrelevant for the present discussion.

The second distinction is between true carcinogens (such as 3,4-benzpyrene, 20-methylcholanthrene and 1,2,5,6-dibenzanthracene), which are potentially able to produce tumors wherever applied or injected, and agents which are incapable of producing tumors except at certain definite sites, irrespective of the manner of administration. The best known examples of the latter are the estrogens (producing tumors from mammary epithelium), betanaphthylamine (producing tumors from the epithelium of the urinary bladder) and orthoaminoazotoluene, paradimethylaminoazobenzene, 2-aminofluorene and 2-acetylaminofluorene (producing tumors in the liver).

A plausible, though admittedly hypothetic, explanation of the tissue specificity in the latter group is that these chemical substances are not themselves carcinogenic but are metabolically converted into carcinogens in the body and that the site of conversion determines the localization of the tumor. Thus the conversion of betanaphthylamine into dibenzcarbazole<sup>19</sup> or some similar compound might occur in the body. Metabolic conversion of an estrogen into a methylcholanthrene-like compound might be possible on the basis of the "theory of disturbed sterol metabolism."<sup>20</sup> On similar lines it is not improbable that the substances which cause hepatic tumors do so by first being metabolically changed in that organ.

If this explanation is correct, these particular substances must be considered as "precursors of carcinogens" rather than as carcinogens proper. It would then be immaterial whether such precursors are irritants or not; the important question would be whether the carcinogens into which they are converted are irritants.

In this connection it is interesting to note (a) that with paradimethylaminoazobenzene the primary effect on the hepatic parenchyma is destructive, leading to secondary proliferative changes,<sup>21</sup> (b) that in patients with occupational tumor of the bladder (now considered to be due to betanaphthylamine<sup>22</sup>) there is abundant

clinical evidence of irritation of the mucosa of the bladder during the preneoplastic stage<sup>11b</sup> and (c) that with estrogens the primary effect on the mammary epithelium is also proliferative (though presumably the multiplication is due to direct stimulation of cells and not reparative in type). The point of interest is that while none of these substances are irritants to ordinary tissues (i. e., at sites of application or injection), they do induce hyperplastic changes in those tissues where tumors ultimately develop.

However, the main problem is concerned with direct carcinogens and with the question whether these can all be classed as irritants. Regarding carcinogens of a physical character there is no dispute, since strong sunlight, ultraviolet rays, roentgen rays, gamma rays, heat and freezing are all irritant according to any definition one may choose. As regards chemical carcinogens, any difference of opinion that may exist arises from confusion as to the meaning of the term "irritation." If by this is meant the production of gross damage of tissue, some carcinogens (e. g., 9,10-dimethyl-1,2-benzanthracene) are irritants, while others (e. g., 1,2,5,6-dibenzanthracene) are not. With most carcinogens, however, the tendency for ulceration to occur is largely dependent on dosage.<sup>23</sup> But if by "irritation" is meant the production of a continued state of reparative hyperplasia, which is the meaning as defined in this review, then all the direct carcinogens, without exception, are irritants.<sup>24</sup> Hyperplasia in fact not only is seen constantly in the preneoplastic stages of carcinogenesis when the carcinogen is known to be operating from outside the body but is also observed prior to the development of tumors in those cases in which the nature of the carcinogen is unknown.

One is thus brought back to the central problem of hyperplasia. What does it represent? How does it differ from neoplasia? And what evidence is there that preneoplastic hyperplasia is biologically different from ordinary (reparative) hyperplasia?

#### THE NATURE OF PRENEOPLASTIC HYPERPLASIA

Hyperplasia is cellular proliferation in excess of the normal. But so is neoplasia. The difference between the two is usually described as being one of control: Hyperplasia is strictly under bodily control and serves a useful purpose; neoplasia is much less under the influence of such control, and in spite of its potential ability

19. Boyland, E., and Brues, A. M.: *Proc. Roy. Soc., London*, s.B **122**:429, 1937.

20. Kennaway, E. L., and Cook, J. W.: *Chem. & Indust.* **10**:521, 1932. Fieser, L. F., in *University of Pennsylvania Bicentennial Conference*, Philadelphia, 1940.

21. Orr, J. W.: *J. Path. & Bact.* **50**:393, 1940. Wolbach, S. B.: *Am. J. Path.* **13**:662, 1937.

22. Hueper, W. C.; Wiley, F. H., and Wolfe, H. D.: *J. Indust. Hyg.* **20**:46, 1938.

23. Shear, M. J.: *Am. J. Cancer* **33**:499, 1938.

24. Pullinger, B. D.: *J. Path. & Bact.* **50**:463, 1940.

to perform some of the specialized functions that are characteristic of its parent tissue, it does not seem to serve a coordinated useful purpose in the body economy.

This distinction is not satisfactory, however. Such terms as "purpose," "intention," "usefulness" and "orderliness" when applied to individual cells or tissues are meaningless. Can we say, for instance, that fibrosis of the heart valve is useful? If so, useful to what? As a stage in the healing of a rheumatic lesion it serves a "useful purpose," but in respect to the subsequent functioning of the heart it is a most unfortunate occurrence. A cell has no "intentions"; it merely possesses specific innate propensities for responding in certain predetermined ways to environmental stimuli.<sup>25</sup>

There is, however, another distinction between hyperplasia and neoplasia, which can be recognized objectively, without having resort to anthropomorphic phraseology. This is concerned with the extent or limit of growth: In hyperplasia the increase in proliferation proceeds up to a point, after which the balance between the rate at which new cells are produced and that at which old ones die off remains at a constant level; in neoplasia the increased proliferation never reaches a permanent level, irrespective of the rate of growth—hence the proliferation is progressive.

Knowledge of the development of occupational tumors in man and of experimentally induced tumors in animals points to the occurrence of "preneoplastic hyperplasia" preceding the development of a tumor. The conclusion already reached that all direct carcinogens are irritants means when translated into terms of response that all tumor-producing agents are also hyperplasia-producing agents. These facts taken together indicate that hyperplasia is an invariable and essential preliminary to neoplasia (des Ligneris<sup>26</sup>). But it has already been shown that not all irritants are carcinogenic. Therefore, preneoplastic hyperplasia must be a special kind of hyperplasia, biologically distinguishable from ordinary (reparative) hyperplasia. Can this conclusion be corroborated by precise experimental evidence?

In a sense, the answer has already been provided in a foregoing section: It has been shown (a) that the hyperplasia induced by a noncarcinogenic irritant does not lead to neoplasia, however long it may be maintained, and (b) that the addition of a nonspecific irritant to a carcino-

genic irritant may actually reduce the carcinogenic potency of the latter. But there is a third and even more precise method of demonstrating that ordinary (reparative) hyperplasia cannot perform the function of preneoplastic hyperplasia.

When a carcinogen is applied at regular intervals to the skin of a mouse, the appearance of a tumor is delayed for many weeks, and it is during this "induction period" that preneoplastic hyperplasia is evident. The length of the induction period varies from animal to animal but, provided a sufficiently large number of animals is used, the average period is constant enough to permit tests of a quantitative character. (If a fairly potent carcinogen, such as 3,4-benzpyrene, is applied at weekly intervals to the interscapular region of the skin in a mouse, the induction period may be as short as five weeks or as long as thirty weeks, but the time elapsed before tumors appear in 50 per cent of a large group of animals is about sixteen weeks.) In order to determine whether non-specific hyperplasia (i. e., hyperplasia produced by a noncarcinogenic irritant) can perform at least part of the function of preneoplastic hyperplasia, all that need be done is to precede the applications of the carcinogen by a course of applications of the nonspecific irritant (say, for ten to twenty weeks) and then note whether the induction period has thereby been shortened. Such experiments have been carried out with several irritants, with negative results (table 2).

Altogether, therefore, the evidence that preneoplastic hyperplasia is of a specific type, distinct from ordinary (reparative) hyperplasia, is convincing.

This conclusion is supported by recent claims that the preneoplastic changes produced by chemical carcinogens are morphologically distinguishable from comparable changes produced by noncarcinogenic irritants, both as regards the hyperplastic epithelium<sup>27</sup> and the fibrotic reactions in the corium.<sup>28</sup>

#### THE MECHANISM OF CARCINOGENESIS

The development of a tumor out of a normal tissue through the action of a carcinogen can be conceived as arising in one of two ways (Deelman<sup>28</sup>): Either the change is a sudden one—a normal cell being converted "at one stroke" into a tumor cell, after which the process of carcinogenesis is virtually completed, the development to a large tumor mass being but a

25. Nicholson, G. W.: *Guy's Hosp. Rep.* **83**:131, 273 and 465, 1933.

26. des Ligneris, M. J. A.: *Am. J. Cancer* **40**:1, 1940.

27. Orr, J. W.: *J. Path. & Bact.* **44**:495, 1938.

28. Deelman, H. T.: *Ztschr. f. Krebsforsch.* **29**:307, 1929.

matter of cell division and growth—or it is dependent on a sequence of separate specific biologic changes, analogous in a sense to a “chain reaction” in a complex chemical synthesis.

The distinction between these two hypotheses has important practical implications. For, if the first hypothesis is correct, one would have to suppose that the necessity for long-continued action of a carcinogen is due to the extreme rarity of neoplastic transformation, and therefore the longer the action the greater the chance of one out of the millions of treated cells undergoing this transformation. On this basis, any modifying influence on the tissue in question before or after the transformation could have but a minor and indirect effect on the progress of the neoplastic process. The term “preneoplastic” would then have meaning only in one sense—that the condition is already biologically neoplastic though morphologically still hyperplastic and that its subsequent progress toward morphologic neoplasia is inevitable and not dependent on the action of a “precipitating” factor. On the other hand, if the second hypothesis is correct, many things could happen between the commencement of carcinogenic action and the fulfilment of the process: The condition might remain at a standstill, awaiting further stimulation by a carcinogen or a “precipitating” factor; the initial stages might conceivably be induced by agents that are not themselves fully carcinogenic, and outside influences might modify the process of carcinogenesis at different stages, both in the sense of augmenting the process and in that of inhibiting it.

Experimental carcinogenesis in animals has helped to solve this important problem, though it cannot be said yet that the accumulated evidence is sufficient to provide an unequivocal answer.

In the neoplastic transformation of the epithelium of the skin of the mouse or the rabbit following application of a carcinogen, three distinct phases are readily recognizable: (1) the prewart stage, also known as the “induction period” of carcinogenesis, during which hyperplasia is the predominant lesion; (2) the stage of benign tumour growth, during which one or more papillomatous structures appear and grow progressively; (3) the stage of cancer, when one or other of the latter structures start infiltrating the subepithelial tissues. (There may be and probably are many more phases involved in carcinogenesis, but these are the three most easily recognized.) The aforementioned distinction between carcinogenesis as a sudden transformation and carcinogenesis as a sequence

of independent reactions can now be presented in a more concrete form: Are the three phases—preneoplastic hyperplasia, wart stage and cancer—consecutive stages of a single carcinogenic process, or are they consecutive but separate processes?

The answer to this question may be sought (a) by determining whether, once the first phase is induced, the other two phases will develop on their own initiative, (b) by investigating the relative extent to which the three phases manifest themselves in different species of animals and (c) by attempting to induce one or the other of the three phases through the action of substances that are incapable of producing all three phases.

The available evidence from the first approach is somewhat ambiguous. It is a well established fact that application of a carcinogen for only a limited period may set in motion a train of events that will ultimately lead to the development of a tumor, long after application of the carcinogen has been discontinued, and that benign tumors induced in this way may later become cancerous without any additional outside influence.<sup>29</sup> In fact, by using a very potent carcinogen, such as 20-methylcholanthrene, a single application is sometimes sufficient to cause a tumor to develop at a much later period.<sup>30</sup> On the other hand, these results are exceptional. In most cases the longer the period of application, the greater is the yield of tumors, the earlier their appearance and the greater the tendency for the benign tumors to become cancerous. Moreover, after the application of the carcinogen has been discontinued, there is a tendency, especially in rabbits, for the warts that have already appeared, to regress, and if in such cases application of the carcinogen is resumed, the warts may be made to reappear.<sup>31</sup>

The balance of evidence is in favor of the view that prior to the establishment of cancer, continued stimulation enhances the carcinogenic process, but there are some contradictions which require further investigation.

The second suggested approach is from the point of view of species response. When two species of animals are treated with the same carcinogen, the relative responses as regards the three phases of carcinogenesis may be different. Both the mouse's skin and the rabbit's skin re-

29. Leitch, A.: *Brit. M. J.* **2**:1101, 1922.

30. Mider, G. B., and Morton, J. J.: *Am. J. Path.* **15**:299, 1939. Cramer, W., and Stowell, R. E.: *Cancer Research* **3**:36, 1943.

31. (a) Rous, P., and Kidd, J. G.: *J. Exper. Med.* **73**:365, 1941. (b) MacKenzie, I., and Rous, P.: *ibid.* **73**:391, 1941.

spond readily to tarring by developing warts in a short time. In the rabbit the induction period with tar is even shorter than that in the mouse; yet in the mouse the warts tend to grow progressively even after application of the carcinogen has been discontinued, while in the rabbit they tend to regress in the absence of continual stimulation; those in the former become cancerous readily and those in the latter only rarely or with difficulty.<sup>31</sup> It has been suggested<sup>32</sup> that these results lend support to the idea of a dissociation of the component phases of carcinogenesis.

The third approach to the problem is the one of most interest in this review, because it is concerned with the influence of noncarcinogenic irritants on carcinogenesis. For convenience the experimental data may be segregated into three groups: (1) The irritant and the carcinogen are applied concurrently (table 1); (2) the irritant is applied for a period preceding application of the carcinogen (table 2), and (3) the irritant is applied after the application of the carcinogen has been discontinued (table 3). (The nomenclature previously introduced by me<sup>32</sup> will be followed here: The change from normal to preneoplastic epithelium is called precarcinogenic action; that from preneoplastic epithelium to the wart state, epicarcinogenic action, and the malignant transformation of a wart, metacarcinogenic action. These terms avoid the use of such cumbersome phrases as "the action that leads to the production of a preneoplastic stage" or "the precipitation of a tumor at the site of a preneoplastic lesion." Other terms that have come into general use are "cocarcinogenic action," meaning the augmentation of carcinogenesis by a noncarcinogenic agent applied concurrently with a carcinogen,<sup>33</sup> and "anticarcinogenic action" meaning the inhibition of carcinogenesis by an agent applied concurrently with a carcinogen.<sup>34</sup> It should be noted that "anticarcinogenic action" does not refer to the power of causing regression or destruction of an established tumor. Similarly, the term "preneoplastic" is not synonymous with "precancerous," the latter referring to all stages prior to cancer. Thus a benign tumor can be precancerous if it has a tendency to become cancerous; it cannot be considered preneoplastic, since it is already a neoplasm.)

The effect of applying another irritant concurrently with a carcinogen (table 1) varies according to the irritant used, from pronounced

inhibition of tumor formation, or anticarcinogenic action (as with mustard gas), to pronounced augmentation of tumor formation, or cocarcinogenic action (as with croton oil). Most irritants seem, however, to have no significant influence on carcinogenesis when applied concurrently with the carcinogen.

These results call for further explanation. When the combined irritative effect on the skin is so severe as to cause gross ulceration, carcinogenesis may be impaired, whatever the irritant.<sup>35</sup> With a true anticarcinogenic agent, however, inhibition occurs even when the combined irritative effect is no greater than that of the carcinogen alone. (This is demonstrated in practice by dilution of both the carcinogen and the irritant to the desired degree.) Conversely, when the carcinogen used is applied in such a form as to produce tumors under optimal conditions, the addition of a cocarcinogen could hardly be expected to cause demonstrable augmentation of carcinogenesis. Therefore, to test for co-carcinogenic action, it is necessary for the carcinogen to be applied in a diluted form.<sup>36</sup> (Compare, for instance, the effect of croton oil in conjunction with concentrated and dilute benzpyrene, respectively.) These complications are no doubt responsible for the conflicting results obtained by different authors using the same irritants.

The results of the aforementioned experiments, in which an irritant and a carcinogen were applied concurrently, supply yet further proof that intensity of irritation is not the deciding factor in carcinogenesis. They bring to light the existence of specific co-carcinogenic agents and equally specific anticarcinogenic agents; they fail, however, to elucidate the mechanisms involved, owing to the complexity of factors operating during the prolonged period of action.

More precise information is derived from experiments in which application of the irritant either precedes (table 2) or follows (table 3) the treatment with the carcinogen: The former (precarcinogenic action) deals with the ability or inability of an irritant to take the place of the carcinogen proper in inducing a preneoplastic hyperplasia; the latter (epicarcinogenic action), with the ability or inability of the irritant to precipitate a benign tumor at the site of preneoplastic hyperplasia.

The results of these two series are strikingly different. Whereas attempts to induce precarcinogenic action on the skin by a noncarcino-

32. Berenblum, I.: *Cancer Research* 1:807, 1941.

33. (a) Berenblum, I.: *Cancer Research* 1:44, 1941. (b) Shear.<sup>33</sup>

34. (a) Berenblum, I.: *J. Path. & Bact.* 40:549, 1935. (b) Berenblum.<sup>18a</sup>

35. (a) Cabot, S.; Shear, N.; Shear, M. J., and Perrault, A.: *Am. J. Path.* 16:301, 1940. (b) Berenblum.<sup>18</sup>

36. (a) Sall, R. D.; Shear, M. J.; Leiter, J., and Perrault, A.: *J. Nat. Cancer Inst.* 1:45, 1940. (b) Berenblum.<sup>32</sup>

TABLE 1.—Cocarcinogenic Action on the Skin (Application of Irritant Concurrently with Carcinogen)

Animal	Carcinogen	Irritant	Result	References
<b>Group B</b>				
Mouse	Tar.....	Heat (70 C.).....	(+)	Derom, E.: <i>Bull. du Cancer</i> <b>13</b> :422, 1924
Mouse	Tar.....	Heat (60-85 C.).....	=	Choldin, E.: <i>Ztschr. f. Krebsforsch.</i> <b>31</b> :545, 1930
Mouse	20-methylcholanthrene	Heat (scalding).....	=	des Ligneris <sup>20</sup>
Mouse	3,4-benzpyrene.....	Heat (cautery).....	=	Brunschwig, A.; Tschetler, D., and Bissell A. D.: <i>Ann. Surg.</i> <b>108</b> :1084, 1937
Mouse	1,2,5,6-dibenzanthracene	Heat (cautery).....	=/+	Lauridsen, J., and Eggers, H. E.: <i>Cancer Research</i> <b>3</b> :43, 1943
Rabbit	Tar.....	Heat (55 C.).....	+	Raposo, S.: <i>Compt. rend. Soc. de biol.</i> <b>98</b> :990, 1928
Mouse	Tar.....	Cold (freezing with solid CO <sub>2</sub> )	+/-/-	Berenblum <sup>26</sup>
Mouse	Tar.....	Ultraviolet rays (mild)...	++	Findlay, G. M.: <i>Lancet</i> <b>2</b> :1070, 1938. Dormanna, E.: <i>Ztschr. f. Krebsforsch.</i> <b>40</b> :577, 1934
Mouse	Tar.....	Ultraviolet rays.....	=	Kohn-Speyer, A. O.: <i>Lancet</i> <b>2</b> :1805, 1929. Teutshländer, O.: <i>Klin. Wchnschr.</i> <b>10</b> :1284, 1937
Mouse	3,4-benzpyrene.....	Ultraviolet rays.....	=	Taussig, J.; Cooper, Z. K., and Seelig, M. G.: <i>Surg., Gynec. &amp; Obst.</i> <b>66</b> :929, 1938. Rush, H. P.; Kline, B. E., and Baumann, C. A.: <i>Cancer Research</i> <b>2</b> :183, 1942
Mouse	20-methylcholanthrene or 9,10-dimethyl-1,2-benzanthracene	Ultraviolet rays.....	=	Rush, H. P.; Kline, B. E., and Baumann, C. A.: <i>Cancer Research</i> <b>2</b> :183, 1942
Mouse	3,4-benzpyrene.....	Strong sunlight.....	---	Doniach, I., and Mottram, J. C.: <i>Am. J. Cancer</i> <b>30</b> :234, 1940
<b>Group C</b>				
Mouse	Tar.....	Scarification.....	=	Roussy, G.; Leroux, R., and Peyre, E.: <i>Bull. du Cancer</i> <b>13</b> :587, 1924
<b>Group D</b>				
Mouse	Tar or 1,2,5,6-dibenzanthracene	Dichlorodethylsulfide (mustard gas)	---	Berenblum <sup>24</sup>
Mouse	Tar.....	Cantharidin.....	---	Berenblum <sup>24a</sup>
Mouse	20-methylcholanthrene	Heptaldehyde.....	---	Carruthers, C.: <i>Arch. Path.</i> <b>30</b> :1134, 1940
Mouse	3,4-benzpyrene.....	Phenolic fraction of tar	---	Shear <sup>23</sup> ; Cabot <sup>25a</sup>
Mouse	3,4-benzpyrene.....	Monochloroacetone and other Cl— derivatives	---	Crabtree, H. G.: <i>J. Path. &amp; Bact.</i> <b>51</b> :308, 1940
Mouse	1,2,5,6-dibenzanthracene	Parathlocresol.....	=	Reimann, S. P., and Hall, E. M.: <i>Arch. Path.</i> <b>22</b> :55, 1936
Mouse	Tar.....	Acetic acid.....	=	Berenblum <sup>24a</sup>
Mouse	Tar.....	Iodoacetic acid.....	=	Berenblum <sup>24a</sup>
Mouse	Tar.....	Trichloroacetic acid.....	=	Berenblum <sup>24a</sup>
Mouse	Tar.....	Turpentine.....	=	Berenblum <sup>24a</sup>
Mouse	Tar.....	Saponated solution of cresol	=	Berenblum <sup>24a</sup>
Mouse	Tar.....	Cyclohexene.....	=/-	Berenblum <sup>24a</sup>
Mouse	3,4-benzpyrene (1%)...	Turpentine.....	=	Berenblum <sup>24a</sup>
Mouse	3,4-benzpyrene (1%)...	Xylene.....	=	Berenblum <sup>24a</sup>
Mouse	3,4-benzpyrene (1%)...	Croton oil.....	=	Berenblum <sup>24a</sup>
Mouse	3,4-benzpyrene (0.03%)	Turpentine.....	=	Berenblum <sup>24a</sup>
Mouse	3,4-benzpyrene (0.05%)	Xylene.....	=	Berenblum <sup>24a</sup>
Mouse	3,4-benzpyrene (0.05%)	Croton oil or resin.....	+++	Berenblum <sup>24a</sup>
Mouse	1,2,5,6-dibenzanthracene (0.3%)	Croton oil.....	=	Berenblum <sup>24a</sup>
Mouse	1,2-benzanthracene (0.3%)	Croton resin.....	=	Berenblum <sup>24a</sup>
Mouse	3,4-benzpyrene (0.2%)..	Basic fraction of tar....	=	Cabot <sup>25a</sup>
Mouse	3,4-benzpyrene (0.05%)	Basic fraction of tar....	++	Shear <sup>23</sup> ; Cabot <sup>25a</sup> ; Sall and associates <sup>26a</sup>
Mouse	3,4-benzpyrene (0.02%)	Basic fraction of tar....	+	Sall and associates <sup>26a</sup>

## Explanatory Notes on Tables 1 to 5

The irritants are divided into group A (chemical carcinogenic agents), group B (physical carcinogenic agents), group C (physical noncarcinogenic agents) and group D (chemical noncarcinogenic agents).

The following experiments referred to in the literature are excluded from the tables: (1) experiments in which the irritant was applied or injected at a different site from that of the carcinogen; (2) experiments in which the irritant (a scarifying agent or a chemical substance with solvent properties) was applied immediately before each application of the carcinogen, thereby facilitating the penetration of the carcinogen into the skin; (3) other experiments in which the conditions were too complex for the results to be interpreted in terms of hyperplasia (e. g., sutures beneath the skin); (4) results reported without details of the experimental procedure.

The following abbreviations are used in the tables: +, ++ and +++ refer to slight, moderate and marked augmentation of carcinogenesis (i. e., earlier appearance of tumors than in controls). —, — and — refer to slight, moderate and marked inhibition of carcinogenesis (i. e., delay in appearance of tumors). = refers to no demonstrable augmentation or inhibition of carcinogenesis. =/+ and =/- refer to such slight augmentation or inhibition of carcinogenesis as to be of doubtful significance. (—), (=) and (+) refer to results (or claims) the significance of which is doubtful either because the numbers of animals used were small or because the controls were inadequate. +(\*) refers to localization of tumors at or near the injury without, however, any shortening in the times of appearance of the tumors as a whole. —/+ refers to inhibition of carcinogenesis at the center of injury and augmentation at the margin of the injury, but no shortening of the time of appearance of tumors as a whole. —(§), =(§) or +(§) refer to information obtained from abstracts, the original papers not having been consulted.

genic irritant (table 2) have so far been almost entirely unsuccessful, positive and in some cases striking results have been obtained when many of these same irritants were tested for epidermal action (table 3). This means that while

Similar experiments on subcutaneous tissues instead of on skin yielded somewhat different results. Thus several workers<sup>37</sup> observed that irritation by nonspecific agents produced precarcinogenic effects if the subsequent carcinogen

TABLE 2.—*Precarcinogenic Action on the Skin (Application of Irritant Before Commencement of That of Carcinogen)*

Animal	Irritant	Carcinogen	Result	References
<b>Group A</b>				
Mouse	3,4-benzpyrene.....	1,2,5,6-dibenzanthracene.	++	Hieger, I.: <i>Am. J. Cancer</i> <b>28</b> : 522, 1936
Mouse	3,4-benzpyrene, 20-methylcholanthrene or, 9,10-dimethyl-1,2-benzanthracene	20-methylcholanthrene, 9,10-dimethyl-1,2-benzanthracene or 3,4-benzpyrene	+++	Lavik, M. S.; Moore, P. R.; Rush, H. P., and Baumann, C. A.: <i>Cancer Research</i> <b>2</b> : 180, 1942. Rush, H. P.; Kline, B. E., and Baumann, C. A.: <i>ibid.</i> <b>2</b> : 183, 1942
<b>Group B</b>				
Mouse	Heat (50 C.).....	Hot tar (70 C.).....	=	Derom, E.: <i>Bull. du cancer</i> <b>13</b> : 422, 1924
Mouse	Heat (60 and 70 C.).....	Hot tar (70 C.).....	(-)	Derom, E.: <i>Bull. du cancer</i> <b>13</b> : 422, 1924
Mouse	Heat (scalding).....	20-methylcholanthrene...	(=)	des Ligneris <sup>38</sup>
Mouse	Cold (freezing with solid CO <sub>2</sub> )	Tar.....	(=)	Parodi, U.: <i>Pathologica</i> <b>16</b> : 175, 1924
Mouse	Ultraviolet rays (mild)...	Tar.....	=	Dormanns, E.: <i>Ztschr. f. Krebsforsch.</i> <b>40</b> : 577, 1934
Mouse	Ultraviolet rays.....	20-methylcholanthrene or 9,10-dimethyl-1,2-benzanthracene	=	Rush, H. P.; Kline, B. E., and Baumann, C. A.: <i>Cancer Research</i> <b>2</b> : 183, 1942
Mouse	Radium (treatment repeated twice during tarring)	Tar.....	=	Roussey, G.; Leroux, R., and Peyre, E.: <i>Bull. du cancer</i> <b>13</b> : 587, 1924
<b>Group C</b>				
Mouse	Scarification (sandpaper)	Tar.....	=/-	Ludford, R. J.: <i>Brit. J. Exper. Path.</i> <b>10</b> : 193, 1929
Mouse	Incision.....	Tar.....	=	von Meyenburg, H., and Fritzsche, H.: <i>Schweiz. med. Wchnschr.</i> <b>73</b> : 201, 1943
<b>Group D</b>				
Mouse	Allyl isothiocyanate.....	Tar.....	=(§)	Sobolewa, N. G.: <i>Vestnik roentgenol. i radiol.</i> <b>4</b> : 191, 1926; abstracted, <i>Cancer Rev.</i> <b>3</b> : 116, 1928.
Mouse	Dichlorodithylsulfide (mustard gas)	Tar.....	=	Berenblum <sup>39</sup>
Mouse	Croton resin.....	3,4-benzpyrene.....	=	Berenblum <sup>39</sup>

TABLE 3.—*Epidermal Action on the Skin (Application of Irritant After Discontinuing That of Carcinogen)*

Animal	Carcinogen	Irritant	Result	References
<b>Group A</b>				
Mouse	Carcinogenic hydrocarbon	Carcinogenic hydrocarbon	+++	See table 2
<b>Group B</b>				
Mouse	3,4,5,6-dibenzacridine....	Light cauterization.....	+(§)	Rondoni, P., and Corbellini, A.: <i>Tumori</i> <b>10</b> : 106, 1936; abstracted, <i>Am. J. Cancer</i> <b>32</b> : 458, 1938
Mouse	Tar.....	Cold (freezing with solid CO <sub>2</sub> )	++	Berenblum, I.: <i>Brit. J. Exper. Path.</i> <b>11</b> : 208, 1930
Mouse	Tar.....	Radium (large dose)....	-	Cramer, W.: <i>Brit. J. Radiol.</i> <b>5</b> : 618, 1932
Mouse	Tar.....	Radium (medium dose of γ rays)	+	Mottram, J. C.: <i>Am. J. Cancer</i> <b>30</b> : 746, 1937
Mouse	Tar.....	Radium (medium dose of β rays)	+	Mottram, J. C.: <i>Am. J. Cancer</i> <b>32</b> : 75, 1938
Mouse	Tar.....	Ultraviolet rays (mild)...	=	Dormanns, E.: <i>Ztschr. f. Krebsforsch.</i> <b>40</b> : 577, 1934
<b>Group C</b>				
Mouse	Tar.....	Single incision.....	++	Deelman, H. T.: <i>Ztschr. f. Krebsforsch.</i> <b>21</b> : 220, 1924. Deelman, H. T., and van Erp, J. P.: <i>ibid.</i> <b>24</b> : 86, 1926
Mouse	Tar.....	Single incision.....	=	Cramer <sup>40</sup>
Mouse	Tar.....	Single incision.....	+(*)	Fullinger, B. D.: <i>J. Path. &amp; Bact.</i> <b>55</b> : 301, 1943
Rabbit	Tar.....	Single incision.....	++	Rous and Kidd <sup>41</sup> ; McKenzie and Rous <sup>42</sup> ; von Meyenburg, H., and Fritzsche, H.: <i>Schweiz. med. Wchnschr.</i> <b>73</b> : 201, 1943
Mouse	Tar.....	Scarification (sandpaper)	-	Ludford, R. J.: <i>Brit. J. Exper. Path.</i> <b>10</b> : 193, 1929
<b>Group D</b>				
Mouse	Tar.....	Dichlorodithylsulfide (mustard gas)	=	Berenblum <sup>39</sup>
Mouse	Tar.....	Allyl isothiocyanate.....	+(§)	Sobolewa, N. G.: <i>Vestnik roentgenol. i radiol.</i> <b>4</b> : 191, 1926; abstracted, <i>Cancer Rev.</i> <b>3</b> : 116, 1928
Mouse	3,4-benzpyrene.....	Turpentine.....	+	Berenblum <sup>39</sup>
Rabbit	Tar.....	Turpentine.....	++	Rous and Kidd <sup>41</sup>
Mouse	3,4-benzpyrene.....	Croton resin.....	+++	Berenblum <sup>39</sup>
Mouse	3,4-benzpyrene.....	Croton oil.....	+++	Mottram, J. C.: <i>J. Path. &amp; Bact.</i> <b>56</b> : 181, 1944

ordinary irritants generally prove unsuccessful in producing a preneoplastic lesion of the skin, many of them seem able to precipitate a tumor once the preneoplastic state has been established.

37. (a) Lacassagne, A.: *Compt. rend. Acad. d. sc.* **196**: 69, 1933. (b) Burrows, H.; Mayneord, W. V., and Roberts, J. E.: *Proc. Roy. Soc., London, s.B* **123**: 213, 1937.

was roentgen rays. With benzpyrene as the subsequent carcinogen, however, negative results were obtained (part 2 in table 4).<sup>38</sup>

Finally, there is the important question of metacarcinogenic action; that is to say, the question whether irritants are capable of accentuating the tendency for a benign tumor to become cancerous. For technical reasons, such experiments are difficult to perform. However, at least four such investigations have been carried out with heat (cauterization and scalding), croton resin and turpentine, respectively, as the irritants. The data on the effects of scalding published by des Ligneris<sup>26</sup> are presented in table 5 in a form in which they can be readily

made on its significance in relation to the "somatic mutation theory of cancer."<sup>40</sup> It would seem, if the foregoing conclusions are accepted, that this theory would have to be modified in the sense of postulating a series of separate consecutive mutations for production of a fully established cancer. Though this theoretically is not impossible, it would tend to strain the theory somewhat.

#### COMMENT AND CONCLUSIONS

"The difficulty in most scientific work lies in framing the questions rather than in finding the answers, and by the time we are in a position to know what the crucial question really is we have generally pretty well got the answer." This

TABLE 4.—Co-carcinogenic Action (Part 1) and Precarcinogenic Action (Part 2) on Subcutaneous Tissue

Animal	Irritant	Carcinogen	Medium	Result	References
Part 1					
Mouse	Basic fraction of tar	3,4-benzpyrene (1 mg.)	Lard	=/-	Sall and associates <sup>39a</sup>
Mouse	Basic fraction of tar	3,4-benzpyrene (0.5 mg.)	Lard	=	Sall and associates <sup>39a</sup>
Mouse	Basic fraction of tar	3,4-benzpyrene (0.1 mg.)	Lard	+ + +	Sall and associates <sup>39a</sup>
Mouse	Basic fraction of tar	3,4-benzpyrene (1%)	Cholesterol	=	Sall and associates <sup>39a</sup>
Mouse	Basic fraction of tar	1,2,5,6-dibenzanthracene (0.1 mg.)	Lard	+ +	Sall and associates <sup>39a</sup>
Mouse	Basic fraction of tar	20-methylcholanthrene (0.1 mg.)	Lard	=	Sall and associates <sup>39a</sup>
Mouse	Basic fraction of tar	20-methylcholanthrene (0.02 mg.)	Lard	=/-	Sall and associates <sup>39a</sup>
Mouse	Basic fraction of tar	9,10-dimethyl-1,2-benzanthracene (0.05 mg.)	Lard	+	Sall and associates <sup>39a</sup>
Mouse	Mechanical injury	20-methylcholanthrene (10 mg.)	(? glycerine)	=	Shear <sup>28</sup>
Rat	Croton resin	3,4-benzpyrene (2.5 mg.)	Sesame oil	=	Berenblum <sup>32</sup>
Rat	Croton resin	3,4-benzpyrene (0.05 mg.)	Sesame oil	=	Berenblum <sup>32</sup>
Rat	Croton resin	3,4-benzpyrene (0.001 mg.)	Sesame oil	=	Berenblum <sup>32</sup>
Rat	Turpentine	3,4-benzpyrene (2.5 mg.)	Sesame oil	=	Berenblum <sup>32</sup>
Rat	Turpentine	3,4-benzpyrene (0.05 mg.)	Sesame oil	=	Berenblum <sup>32</sup>
Rat	Turpentine	3,4-benzpyrene (0.001 mg.)	Sesame oil	=	Berenblum <sup>32</sup>
Mouse	Turpentine	3,4-benzpyrene (1 mg.)	Olive oil	=	Beck <sup>38</sup>
Part 2					
Rabbit	Kieselguhr (purified siliceous earth)	X-ray (600 r)		+ + +	Lacassagne <sup>37a</sup>
Rabbit	Kaolin and silica	X-ray (600 r)	Olive oil	+ + +	Burrows and associates <sup>37b</sup>
Mouse	Turpentine	3,4-benzpyrene (1 mg.)	Olive oil	=	Beck <sup>38</sup>

compared with my data on croton resin.<sup>32</sup> In both of these experiments the irritant was applied to the surface of the wart. In those of Cramer<sup>30</sup> the cauterization was applied to the base of the wart, from underneath.

These results show that both heat (which is itself mildly carcinogenic) and croton resin (which is noncarcinogenic) can facilitate to a striking degree the conversion of a benign epithelial tumor into a cancer. The result with turpentine was doubtful.

The balance of evidence is therefore strongly in favor of the view that the component phases of carcinogenesis are consecutive but independent processes.<sup>32</sup> The significance of this conclusion in relation to the etiology of tumors cannot be discussed fully here, but brief comment may be

shrewd observation by Boycott<sup>41</sup> is particularly applicable to the subject of this review.

Many books and reviews and innumerable other publications have appeared from time to time with the set purpose of finding a solution to the problem of the part played by irritation in the development of a tumor. Some of these publications are noteworthy for the patience and the care displayed by the authors in searching through the literature for all references that may have any bearing on the problem. Unfortunately, such reviews commonly suffer from insufficient critical judgment, whether dealing with mere expressions of opinion, with casual observations or

40. Ludford, R. J.: *Scient. Rep. Invest. Imp. Cancer Research Fund* 9:121, 1930. Lockhart-Mummery, J. P.: *The Origin of Cancer*, London, J. & A. Churchill, 1934.

41. Boycott, A.: *Smithsonian Inst. Ann. Rep.*, 1929, p. 323.

38. Beck, S.: *Brit. J. Exper. Path.* 19:319, 1938.

39. Cramer, W.: *Brit. J. Exper. Path.* 10:335, 1929.

with detailed results obtained from statistical analyses. Some publications place critical judgment in the forefront of the work, but among these the "judgment" is sometimes carried too far, tending toward irrational skepticism. Publications confined to statistical analyses are more useful, provided the nature of the irritant is carefully specified in every case and the other postulates are rigidly applied. But most publications are concerned with a few cases personally observed by the authors and with such citations from the literature as happen to support the particular thesis they wish to stress.

Perhaps the fault of the majority of publications on the subject lies in the fact that the

particular questions posed have yielded certain answers. These may now be recapitulated in brief.

Every carcinogen that produces a tumor at the site of application or injection is an irritant in the sense that it induces a continued state of reparative hyperplasia. Furthermore, in all cases where sufficiently accurate observations can be made, it is seen that the primary tumor is preceded by a stage of hyperplasia. From these facts it is concluded that hyperplasia is an essential precursor of neoplasia. But it is now certain that only some, not all, irritants are carcinogenic. Therefore, preneoplastic hyperplasia must be a specific type, biologically (and, it is claimed, even morphologically) distinct from ordinary reparative hyperplasia.

Hence, there is no simple answer to the simple question: Is irritation the cause of cancer? Once the term "a specific form of irritation" is introduced, the problem ceases to be simple.

The problem is even more complicated than that. There is good reason to believe that carcinogenesis is not a single process but consists of several component phases which may be dissociated; so that in discussing the role of irritation in carcinogenesis it is necessary to inquire whether an irritant can be responsible for some of the component phases even when it cannot produce them all.

Fortunately, from experimental studies on animals evidence is now available which throws light on this problem, though more information is required before the tentative conclusions reached are fully established.

The evidence indicates that preneoplastic hyperplasia is a highly specific type of hyperplasia, since only carcinogenic irritants can produce it with certainty, but that once the preneoplastic state has been induced (by a true carcinogen) a benign tumor can be made to appear at that site, and a tumor already present can have its progress to carcinoma hastened, by the action of a variety of noncarcinogenic irritants.

If this is confirmed, the following practical lessons will have been learned: (a) that there is little danger of an ordinary irritant producing a tumor of its own accord; (b) that this applies also to the initiation of a preneoplastic lesion; (c) that, given a preneoplastic lesion, the subsequent development of a benign tumor at the site may be facilitated, and its progress to cancer hastened, by the action of a variety of non-specific irritants. It is a comforting thought, however, that with most nonspecific irritants this facilitation is far less effective than it is with a true carcinogen.

TABLE 5.—Application of Irritant After Development of Wart (Test for Metacarcinogenic Action)

Carcinogen Used to Produce Wart	Subsequent Irritant	Result (Carcinoma)	Reference
Group B			
Tar.....	Cauterization of base of wart	++	Cramer <sup>20</sup>
20-methylchol-anthrene	Repeated scalding	+++	des Ligneris <sup>22</sup>
Group D			
3,4-benzpyrene	Turpentine	=/+	Berenblum <sup>22</sup>
3,4-benzpyrene	Croton resin	+ +	Berenblum <sup>22</sup>

Analyses of results of (a) des Ligneris (scalding) (b) Berenblum (croton resin)					
Mice Used	Irritant	Survivors	Number in Which Lesion Became Cancerous or Translational	Number in Which Tumor Remained Benign	Number in Which Tumor Regressed
a 1 30	0 (control)	36	6 (17%)	11 (30%)	19 (53%)
a 2 40	Scalding	32	20 (62%)	7 (22%)	5 (16%)
b 1 20	0 (control)	17	8 (47%)	1 (6%)	8 (47%)
b 2 20	Croton resin	18	14 (78%)	3 (17%)	1 (5%)

question posed—Is irritation the cause of tumor formation?—is too simple. The result of such an inquiry tends to resolve itself into a statement as to how many authorities are for this view and how many are against. Unfortunately, decision by majority is not the best means of establishing scientific truth.

In the present review an attempt has been made to probe more deeply into the problem by framing more elaborate questions than most previous authors have propounded. But this has been possible only by making certain initial assumptions—for instance, that any effect irritation might have on carcinogenesis is through the reparative hyperplasia which it induces. To this extent the inquiry is artificial. Alter these premises, and the problem changes. However, within the framework of these premises the

## ARTERIOSCLEROSIS

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(Continued from page 181)

### THE ANOXEMIA THEORY

VASOTONIA: B. HYPERTONIA FOLLOWED BY CONSTRICTION ANOXEMIA;  
AGENTS AND INFLUENCES PRODUCING IT

Hypertonic agents elicit a contraction of the muscular elements of the vascular walls and thereby a reduction of the vascular bed necessitating a compensatory acceleration of the speed of blood flow through an increase of the dynamic blood pressure, i.e., hypertension. Under these conditions the contractile components of the vascular wall carry the main functional load, as the elastic elements in a contracted vessel are relaxed, showing a close and densely wavy appearance. It stands to reason that prolonged or frequently recurring excessive contractions of the arterial walls effect a disturbance of the nutritive conditions and the oxygenation of the tissues and thereby elicit regressive changes. The following causative mechanism is active: Inordinate vasoconstrictions result in a reduction of the blood flow of the vasa vasorum, as these are compressed by the contracting media, causing thereby, especially in the inner portions of the vascular wall, ischemic hypoxemia with accumulation of metabolic waste products. There is, moreover, increased production of these metabolites because of the extraordinarily marked functional activity of the muscle cells. The increased density of the contracted vascular structures hinders adequate movement of the tissue fluids and reduces processes of diffusion. The ensuing injury to the vascular tissues, especially their sensitive endothelial lining, leads finally to increased permeability with subsequent infiltration by constituents of the plasma, thereby preparing the way for secondary degenerative and necrotizing reactions as well as proliferative responses (edematous sclerosis).

The validity of this conception is attested by the dynamic conditions present in the hearts of animals subjected to lethal poisoning by parathyroid hormone (Hueper), vitamin D, and digitalis glucosides (Levitski; Bauer; Hu, Lieu and Li; Lendle; Korth and Spang; Lindner; Büch-

ner; Weese and Dieckhoff; Hueper and Ichniowski), which leads to myocardial as well as arteriolar lesions. In an evaluation of the causative factors responsible for the hemorrhages and the myocardial necroses observed under these conditions, it is significant that the topographic relations of the myocardial arteries and arterioles to the surrounding muscular tissue of the heart are approximately the same as those of the vasa vasorum to the muscle tissue of the arterial media. The cardiac effect elicited by excessive doses of the three substances mentioned consists of an extraordinary prolongation and accentuation of the systolic contraction and an incompleteness and shortening of the diastolic dilatation of the ventricles. Normally the circulation in the coronary arterial system is at a standstill during the peak of the systole, because the coronary arterioles are compressed by the bulges of the contracting myocardium (von Anrep; Fock). It is obvious that the lengthening of the systolic phase associated with an exaggerated myocardial contraction creates a state of circulatory stasis in the myocardial vessels resulting in turn in the production of myocardial anoxemia, which is most pronounced in those parts of the myocardium located near or beyond the end of the blood supply line, i.e., the subendocardial and papillary regions where the ischemic necroses and hemorrhages are seen. It may be added that similar myocardial changes occur in connection with epinephrine poisoning (Franz; Josué; Fischer-Wasels; Ziegler; Stief and Tokay; Iwanowsky; Fleisher and Loeb, and others) on a functional vasospastic basis.

In contrast to the rather recent establishment of relations between vascular hypotonia and the genesis of arteriosclerotic lesions, causal connections between arterial hypertonia and arteriosclerosis have been recognized for many years, as numerous clinical as well as experimental observations link arteriosclerotic and arterionecrotic

changes with the action of agents affecting the vascular tonus and the circulation of the blood.

Since such changes when they are sufficiently widespread modify the blood pressure by determining the peripheral resistance to the blood flow, many investigators consider arterial hypertension as the main causal factor of degenerative vascular disease (Mönckeberg). However, in evaluating such relations one must give attention to the fact that increased blood pressure is not always the result of pathologic functional constriction of the peripheral arterioles but may result from other causes, such as increased pumping of the heart, elevation of blood volume, increase in the viscosity of the blood or reduction of the elasticity of the vascular walls. It is probably for these reasons that there are cases on record in which hypertension was present for several years without being accompanied by arteriosclerosis at autopsy (Hick). On the other hand, it is well established that extensive arteriosclerotic changes may be found in persons without hypertension. Such observations may be attributable to the absence of a hypertonic causal mechanism in these particular instances or to the presence of hypertonic influences of such restricted regional type that they were not reflected by elevation of the general blood pressure (Pal). The apparently contradictory nature of these findings has given rise to the claims that hypertension and arteriosclerosis are merely coincidental phenomena caused by the same agent (Davis and Klainer) and that hypertension is the result of arteriosclerosis (Moritz and Oldt; Scott).

Hueck, on the other hand, asserted that arteriosclerosis does not include the hyperplastic vascular reactions associated with hypertension. Inasmuch as the chief functional and metabolic strain in arterial hypertonia is placed on the muscularis of the media, it is only natural that the degenerative and necrotic vascular changes following acute and severe hypertonic episodes involve most prominently the media of the large arteries. A milder continuous or often repeated action of such factors, on the other hand, manifests itself in the appearance of intimal as well as medial reactions of a degenerative and proliferative nature and is apparently the most frequent cause of the sclerotic type of arterial disease affecting both the large and the small vessels.

Vasoconstricting pressor substances are partly of endogenous, partly of exogenous origin. Endogenous agents of this type are produced normally in the thyroid and the parathyroid glands, in the adrenal glands by both the medulla (epinephrine) and the cortex, and in the posterior por-

tion of the pituitary gland (pitressin). A pressor principle is generated by normal kidneys (renin) and especially by ischemic kidneys (angiotonin). It may be mentioned that apparently intermediaries of melanin (tyramine, tyrosine), which are chemically related to epinephrine, are also capable of producing hypertension, as melanosis with bilateral metastatic destruction of the adrenal glands has been observed repeatedly in association with marked and persistent elevation of blood pressure.

The majority of the exogenous hypertensive agents are derived from vegetable matter (ephedrine, ergot, digitalis, physostigmine, nicotine, hydrastine); others are of chemically related nature but of synthetic type (amphetamine, desoxycorticosterone, vitamin D, calcium salts, hypercalcemic acidotic chemicals, S-methyl isothiurea and others) or are metals (lead, barium chloride). Physical agents with vasoconstricting properties are cold, trauma (vibration), electric current and solarization. Additional hypertonic factors are represented by psychic strain and chemoallergies. It may be mentioned that carbon monoxide, benzene and aniline poisonings are sometimes followed by hypertensive states (Kemkes; Staemmler and Parade; Mytnik and Genkin; Griesbach) of apparently centrogenic origin.

It is apparent from this long list of endogenous and exogenous vasopressor agents that constitutional anomalies of endocrine nature, hyperplastic and neoplastic reactions affecting the pituitary, adrenal, thyroid and parathyroid glands, renal diseases of various genesis and a large number of environmental, physical and chemical factors, many of which are of occupational significance, are involved in the production of local or generalized vasoconstrictory conditions and furnish thereby the functional basis for subsequent anatomic arteriosclerotic lesions.

#### VASOTONIA: B. HYPERTONIA FOLLOWED BY CONSTRICTION ANOXEMIA

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#### ENDOGENOUS AND EXOGENOUS AGENTS.—

**Epinephrine.**—Epinephrine is a powerful vasoconstricting agent acting especially on the cutaneous, cerebral, renal and splanchnic vessels, while the arteries of the skeletal muscle become dilated. The vasotonic effect on the coronary arteries varies with the species. The considerable shift in the mass of blood entailed thereby is accompanied by a marked rise in blood pressure and an acceleration of the heart action. A rapid liberation of epinephrine from the adrenal medulla into the venous blood occurs under the influence of acute psychic stimuli, physostigmine, morphine, strychnine, pilocarpine, caffeine, narcotics, suffocation, physical labor and nicotine, and in connection with pheochromocytoma of the adrenal gland (Erdheim). Similar vasotonic hypertensive episodes can be elicited by the parenteral introduction of epinephrine.

Josué in 1903 produced degenerative aortic lesions in rabbits by repeated intravenous injections of epinephrine hydrochloride. Numerous investigators have confirmed this observation (Külbs; Fleischer; Thorel; Baylac; Falk; B. Fischer; Albarède; Lissauer; Klieneberger; Emmert; Erb Jr.; Orlowsky; Toropow; Schiro-

kogoroff; Starokadomsky; Kalamkarow; Stief and Tokay; Waterman; Heusner; Ziegler; Rzetkowski; Pearce and Stanton; Scheidemandel; Lortat-Jacob and Sabaréanu; Loeb and Githens; Pic and Bonnamour; Baylac and Albarède; Loeper; Hedinger; Braun; von Korányi; Biland; Torri; d'Amato; d'Amato and Flagella; Trachtenberg; Aschoff and Cohn; Iwanowsky; Hornowski and Nowiski; Boveri; Handelsman; Kaiserling; Pearce and Baldauf; Loeb and Fleisher; Cummins and Stout; Mühlmann and Sehmel; Sturli; Lange; Miller; Kubo; Otto). The experimental methods employed by Josué and the majority of the subsequent workers were such that one, several or many acute and severe episodes of hyperadrenalism were elicited by the intravenous introduction of highly excessive amounts of epinephrine, causing thereby degenerative and necrotic arterial reactions of the acute type. Lange demonstrated that a single powerful dose of epinephrine may occasionally cause medial necrosis. A few investigators (Braun; Lange), on the other hand, administered small daily doses over a prolonged period and thus were able to produce arterial lesions of a more gradual development and of a more chronic variety.

In rabbits which receive intravenous injections of epinephrine hydrochloride there appear first faint gray longitudinal stripes in the intima of the aorta without intimal thickening. The changes involve mainly the ascending and the thoracic aorta. Later irregular depressed and confluent areas of pearly gray color, brittle consistency and mild to moderate elevation are seen. Such lesions are almost always calcified. Finally the aorta becomes an irregularly distended, nodulated tube with numerous circumscribed sacculations. Irregularly outlined and sized nodular plaques project into the lumen. Their centers are often indented. These plaques, firm, hard, shiny and partly discolored brownish, are arranged either in groups or in longitudinal lines. During the course of the changes described, dissecting aneurysms may develop. The carotid, crural, mesenteric and renal arteries often show thickened walls but are usually without calcifications. Histologically there appears first a focus of rapid necrosis of the muscularis with homogenization and disintegration of the muscle cells, followed quickly by calcification of the necrotic matter. The elastic membranes lose their undulation and become more densely packed because of the reduction in the intervening necrotic contractile material. Later on the elastic fibrils also show signs of degeneration (swelling, fusion, fragmentation, granulation, clumping). The intima becomes hyper-

plastic, fibrous and hyaline in places where the arterial wall is sacculated but remains normal above medial necrosis except for some fibrous thickening in the marginal portions of such lesions. Subsequently, around the calcified plaques, reactive inflammatory manifestations develop. Closely packed spindle-shaped cells, sometimes mixed with giant cells, make their appearance in the periphery of the plaques. A cartilaginous transformation of such regressing plaques occurs occasionally (Otto; Erb). While Külbs and Erb did not see any abnormality in the vasa vasorum, Otto and Orłowski noted obliterative endothelial proliferations in the nutritive vessels of the aorta. The aortic degenerative reactions are not regularly elicited in all rabbits but only in a certain percentage of the animals thus treated—16 per cent (Jebrowsky) to 100 per cent (Külbs; Erb; von Korányi; Baylac and Albarède).

Endarteritic processes are present in the pulmonary and coronary arteries (Scheidemandel; Iwanowsky), while the basal cerebral arteries show a thickening of the media composed of swollen cells with pyknotic or swollen nuclei and indistinct outlines. The intercellular spaces are filled with debris (Stief and Tokay). Perivascular cellular accumulations may accompany the changes in the vascular walls. The small organic arteries are usually without pathologic reactions.

In dogs similarly treated with repeated intravenous injections of excessive doses of epinephrine hydrochloride Fischer and Pearce and Stanton did not see any arterial lesions. On the other hand, Otto, who extended such administrations over a period of five to twelve months, found fibrous thickening of the intima and granular lytic degeneration of the media. In the abdominal aorta there were large regressive medial foci beneath intimal nodular thickenings. The endothelium of the vasa vasorum was sometimes much swollen. The intima around the intercostal arterial orifices was thickened. Similar but less severe lesions were present in the innominate artery. Enger, who treated 4 dogs intravenously with epinephrine hydrochloride for periods of from eight months to about two years, observed that the walls of the retinal vessels were thickened and their lumens narrowed, while the renal arterioles occasionally exhibited fatty and amyloid changes. Tarantini noted in 3 dogs given epinephrine by injection only two lentil-sized thickenings of the aortic intima. Erb used 2 monkeys, with negative results.

Ziegler, as well as Pearce and Baldauf, contended that these more or less acute aortic

medial necroses are the result of ischemia from circulatory disturbances in the vasa vasorum in connection with vascular spasm. Erdheim also emphasized this mechanism and mentioned especially the impairment of blood exchange in the walls of the ischemic vessels.

According to Hedinger, Baduel, Ziegler, d'Amato and Flagella and Tarantini, epinephrine hydrochloride injected subcutaneously into rabbits elicited aortic lesions of the described type; Josué, Fischer and Külbs reported failures. Intratracheal instillations of epinephrine gave positive results in rabbits, according to Külbs; such treatment was without effect in the hands of Kaiserling. The intraperitoneal introduction of epinephrine in rabbits was followed by aortic lesions, according to Fischer and Erb. The intramuscular injection of this substance gave positive results, according to Klotz, and negative ones, according to Külbs.

As these acute vascular reactions in their morphologic character differ distinctly from those seen in ordinary human arteriosclerosis of the aorta, most investigators have concluded that acute epinephrine-induced sclerosis is not comparable to the human sclerosis and that therefore no etiologic relations exist between hyperfunction of the adrenal medulla and the development of human arteriosclerosis. It has been generally conceded, however, that acute epinephrine-induced arterionecrosis has a certain resemblance to arteriocalcinosis of the Mönckeberg type.

The experiments of Braun, as well as those of Lange, with rabbits have shown, on the other hand, that very small amounts of epinephrine hydrochloride when injected over a long period elicit marked fibrous intimal thickenings in the aorta and in the renal, the tibial and the pulmonary arteries. In the small pulmonary arteries these thickenings are so severe that the lumens are almost completely obliterated. The lesions are very similar to the arteriosclerotic lesions observed in large and small arteries of man. The observations illustrate the principle observed before, in connection with the action of hypotensive agents, that highly excessive doses produce acute medial degenerations and necroses, while small or moderate doses cause primarily fibrous intimal thickenings.

Additional evidence confirming this contention is supplied by the arterial changes observed in connection with epinephrine-generating tumors (pheochromocytoma) of the adrenal medulla, as well as after repeated and prolonged administration of epinephrine for therapeutic purposes; in both instances one observes the production of paroxysmal hypertension and symptoms like those of Raynaud's disease. Severe and general-

ized arteriosclerosis and arteriolosclerosis, often combined with nephrosclerosis (Paul; Biehl and Wichels; Wiesel; Kremer; Hoffmeyer; Nuzum and Dalton; Raab; Erdheim; Jergensen; Eisenberg and Wallerstein; Kalk; Howard and Barker; Popken; Wells and Boman; Hegglin and Nabholz; Mainzer; Moltchanoff and Davydovsky; Büchner; Fuller; Kirshbaum and Balkin; Schroeder; Hick; Foucar), were noted in many instances. Coronary sclerosis was often present. While the renal arterioles not infrequently contained fatty material in their thickened hyaline intima, and whereas older intimal lesions in the aorta and larger arteries of such patients sometimes showed fatty degenerated foci, there was in general mainly a fibrosing and hyaline type of intimal thickening in the large, medium and small arteries, particularly of young persons (Hoffmeyer; Kahlau; Jergensen; Howard and Barker). It appears probable that the hypercholesteremia, not infrequently accompanying the nephrosclerosis and secondary persistent hypertension, played a part in the production of the lipoidal intimal deposits. Medial changes, rarely of the calcified type, were occasionally seen in large and medium-sized arteries. Paul noted that small arteries showed as an early change a serous imbibition of their walls. The imbibed proteinic matter later solidified and converted the vessels into hyaline tubes. The cerebral arteries exhibited endarteritic lesions.

It is obvious from these data that chronic hyperadrenalism may result in arteriosclerotic and arteriolosclerotic lesions in both man and experimental animals. The significance of the adrenal medulla in the production of hypertension and subsequent arteriosclerosis is illuminated by the fact that the Goldblatt type of experimental renal hypertension does not result after adrenalectomy. It is, however, unlikely that hyperadrenalism is a prominent cause of arteriosclerosis in man, as suggested by Goldzieher, Paul, Fischer-Wasels, Marchand and recently implied again by Raab. There is no reliable evidence indicating the presence of a hyperplastic or hyperactive adrenal gland in the great majority of cases of human arteriosclerosis. While von Lucadou observed an enlarged adrenal medulla in cases of chronic hypertension, absence of an increased epinephrine content of the blood militates against the existence of such a relationship (Mönckeberg; Jores; Eisenberg and Wallerstein).

It is interesting to note that Zinck compared the mucoid-cystic degeneration or disseminated medionecrosis of the aorta seen in man after shock caused by burns with the lesions observed in man after severe injury from epinephrine, while Erdheim mentioned the similarity between

medial injury due to hyperadrenalism and idiopathic cystic medionecrosis of the aorta.

Hirsch and Thorspecken, Heusner and Cyon attempted, unsuccessfully, to accentuate the vascular effect of epinephrine by cutting the vasodepressor nerves. Similar negative results were obtained by Heusner when rabbits given injections of epinephrine hydrochloride were suspended by the hindlegs. These observations led Heusner to the conclusion that a mere increase in blood pressure does not cause medial necroses and that the effect of the epinephrine was therefore a purely toxic one. Loeper, as well as Boderi, hastened and accentuated the medial calcinosis in rabbits treated with epinephrine by feeding calcium salts.

Various procedures have been used in attempts directed at prevention of the development of epinephrine-induced sclerosis with partly contradictory results. Lortat-Jacob and Sabaréanu reported that thyroidectomy prevents the development of epinephrine-induced sclerosis, while castration favors it. Loeb and Githens, on the other hand, could not confirm the inhibitory action of thyroidectomy in this respect. Von Korányi, Loeb and Fleisher and Boveri claimed that iodized sesame oil exerted a preventive or mitigating action. The results of Klieneberger, as well as those of Kalamkarow with the same iodine preparation were inconclusive. A somewhat more definite preventive action seems to have been exerted by potassium iodide or sodium iodide as employed by Cummins and Stout, Loeb and Fleisher, Kubo and von Korányi. Strauss reported a favorable effect in the prevention of epinephrine-induced sclerosis from the administration of a potassium iodide-colloidal silver preparation. Loeb and Fleisher made the same observation when larger doses of potassium iodide were given. Biland, on the other hand, reported an accentuation of the arterionecrotic effect of epinephrine with potassium iodide. Hedinger, as well as Loeb, claimed that potassium iodide is epinephrine-like in its action. Klotz found that the epinephrine effect was not prevented by glyceryl trinitrate. Miller recorded a similar negative result with the use of another vasodepressant, amyl nitrite. Mansfeld, on the other hand, claimed success in this respect for choline. Lang and Szenthe gave insulin to one series of rabbits before the injection of epinephrine hydrochloride to counteract the effect of the epinephrine with a parasympathetic stimulant. A second set of rabbits treated with epinephrine received ergotamine, which paralyzes the sympathetic nerve endings. The aortas of both series of rabbits were grossly and microscopically normal.

Mironescu used without success the vasodepressant eucatropine hydrochloride. Benecke found normal aortas in 2 rabbits treated with epinephrine and spermine, an antagonist of epinephrine. The contradictory or unconfirmed nature of most of the claims made and the use of relatively small series of animals in the experiments do not permit any definite conclusions as to the actual effectiveness of the agents tried.

It is not likely that any colloidal plasmatic disturbances, particularly of the cholesterol content, are involved in the production of epinephrine-induced sclerosis. Lang and Szenthe found that the cholesterol values for their epinephrine-treated rabbits showed irregular and inconsistent fluctuations, while the values of the plasma proteins, albumin, globulin and fibrinogen, remained within normal limits. Bruger and Mosenthal also did not observe any appreciable change of plasma cholesterol following injection of epinephrine hydrochloride in 5 of 6 normal men. Alpern, Tutkewitsch and Besuglow saw in dogs after injection of epinephrine hydrochloride a reduction in the total and the neutral blood lipids, while Hueck noted after adrenalectomy an increase in the free and the esterified cholesterol in the blood.

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**Physostigmine.**—Miller, using rabbits, injected physostigmine (1 mg.) intravenously and observed a gradual moderate rise in blood pressure, which returned to normal in six to eight minutes. This vascular action is a direct muscular one. The injections were given daily for eight weeks. Two of 4 rabbits thus treated showed a focus of medial degeneration in the ascending aorta, which appeared as a moundlike elevation. One of the lesions contained a calcareous deposit. This arteriosclerogenic effect of physostigmine is probably related to the liberation of considerable amounts of epinephrine from the adrenal medulla under the effect of the drug given (Erdheim).

**Physostigmine:**

- Erdheim, J.: *Virchows Arch. f. path. Anat.* **276**:187, 1930.
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**Nicotine.**—Nicotine, which is contained in tobacco used for smoking, chewing and sniffing and which is employed in the production of nicotinic acid and as an insecticide in horticulture, represents the type of vasoconstrictory agent that causes the adrenal medulla to release epinephrine into the blood. The vasopressor action of nicotine is thus the result either of a direct effect on

the vessels or of an indirect one through its influence on the vasomotor centers of the medulla oblongata or on the adrenal medulla, with liberation of epinephrine. Straub and Amann showed that nicotine exerts a pressor effect independent of that from epinephrine. Nicotine may also elicit allergy with the vascular system as the shock organ.

Experimental studies on rabbits showed that degenerative arterial lesions of the type seen in acute epinephrine-induced arteriosclerosis could be readily produced by repeated intravenous, subcutaneous, oral or respiratory introduction of nicotine or nicotine-containing substances (tobacco extract and smoke) (Josué; Gouget; Boveri; Adler and Hensel; Adler; Baylac; Lesieur; Guillan and Gy; von Zebrowski; Gotsev; Lee; Schmiedl; Kosdoba; Kriloff; Starokadomski; Miller; Papadia; Thienes and Butt; von Otto; Ollendorff; Rickett; Loeper and Boveri; Favarger; Krylov). Arteries of similarly treated rats, however, remained intact (Staemmler; Thienes and Butt; Wilson, McNaught and DeEds) in spite of the appearance of adenomatous proliferations in the medulla of the adrenal gland (Staemmler). This observation led Staemmler to the conclusion that rats are refractory to epinephrine and nicotine in vascular respects. Subsequent investigations of Hueper showed that if rats are treated subcutaneously with adequate amounts of nicotine over a sufficiently long period, degenerative and proliferative lesions develop in the aorta and the muscular arteries and arterioles of the heart, the kidneys, the lungs and the brain. Similar observations were made in young dogs given daily injections for a period of ten months.

Among the vascular changes a prevalence of medial necroses and calcinosis of the aorta and other large vessels, with or without secondary intimal thickenings, was noted, identical with those present in acute epinephrine-induced sclerosis. Kosdoba recorded similar medial changes observed in the walls of the large veins. Coronary and myocardial vessels occasionally revealed fibrous or hyaline intimal thickenings some of which caused complete obliteration of the lumens (Kosdoba; von Otto). Schmiedl found small calcified plaques in the renal arteries. In the rats studied by Hueper the arterioles of the brain, the heart, the kidneys and the lungs exhibited edematous and hyaline thickening of the media with occasional focal accumulations of large round or oval nuclei. The aorta was normal except for some medial edema. Small polypous endothelial proliferations were found in the pulmonary arteries. The aortas of 2 dogs showed

medial edema, and one had a large hyaline medial scar and a subendothelial hyaline thickening of the intima. The intima of a renal artery revealed a mushroom-like proliferation of the intima, while the myocardial arteries were not infrequently thickened and had a hyaline swollen media.

The combined treatment of rats with nicotine and mecholyl chloride, two vasotonic antagonists, resulted in a reduction of the degenerative vascular lesions (Hueper). A similar mitigating effect on the severity of the vascular lesions was exerted by a diet rich in two detoxicating agents, ascorbic acid and cystine, fed to the rats which were given injections of nicotine.

Observations made among workers of the tobacco industry as well as among habitual smokers suggest that excessive and prolonged occupational contact with tobacco or nicotine in the form of dust or spray or environmental exposure to these agents in the form of smoke may be etiologically related not only to the development of arteriosclerosis, particularly of the coronary arteries, but also to that of thromboangiitis obliterans (Aschoff; Hilpert; Grotel and co-workers; Strauss; Anitschkow; Koelsch; English, Willis and Berkson; Wright and Moffat; Beneke; von Müller; Moyer and Maddock; Laessing; Weicker; Plenge; Dietrich and Schimert; Külbs, and many others). The statistical and clinical evidence supporting this claim is based in part on the occurrence of functional manifestations, such as angina pectoris, cardiac palpitation, tachycardia or bradycardia, hypertension, transitory amblyopia or hemiplegia, hyperthyroidism and peptic ulcer, attributable to the vasospastic action of nicotine and the high incidence of coronary sclerosis in exposed persons of relatively young age. Grotel and co-workers emphasized that in the series of patients studied by him there was not only a threefold incidence of coronary sclerosis among smokers as compared with nonsmokers but increased frequency and severity of arteriosclerosis of the cerebral vessels among smokers.

The causal role of nicotine in the genesis of thromboangiitis obliterans, an arterial disease which involves most often the vessels of the legs, less often those of the arms and occasionally also those of the mesentery, the heart, the kidneys, the lungs and the brain, is still controversial inasmuch as it is not certain whether nicotine is the primary cause of the arterial changes or only an aggravating and prolonging influence, exerting its effect by means of a chemoallergic mechanism. Many investigators, however, have agreed that the constrictory action

of nicotine on the peripheral vessels plays an essential and primary role and that the inflammatory and apparently allergic phenomena in the vascular walls represent complicating and superimposed reactions of nicotinic or other chemical or physical origin. Cases of thromboangiitis obliterans, often associated with presenile gangrene affecting relatively young men and more or less definitely traced to excessive smoking, have been recorded (Harkavy, Hebal and Silbert; Harkavy; Green; Maddock and Collier; Maddock, Malcolm and Collier; Silbert; Barker; Assmann; Trasoff, Blumstein and Marks; Sulzberger; Schumann, and others). It may be mentioned that Theis and Freeland, as well as Westcott and Wright, disputed the claim that thromboangiitis obliterans is etiologically related to hypersensitivity to tobacco or nicotine, as they did not observe a higher incidence of positive reactions to these agents in patients with thromboangiitis obliterans than in normal persons following cutaneous tests. There has been, nevertheless, almost general agreement as to the fact that continued smoking aggravates thromboangiitis obliterans. Moreover, the action of an allergic factor in the development of this disease is likely not only on morphologic grounds but on the basis that this special type of vascular disorder is causally related to a number of vasotonic agents, such as arsenic, lead and cold, and is always associated with hypersensitivity to cold regardless of the primary cause.

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*Epinephrine Derivatives and Precursors* (Ephedrine, Amphetamine, Tyramine, Pyrocatechin, Tyrosine, etc.).—Many derivatives and

precursors of epinephrine either are primarily hypertonic agents or acquire such sympathomimetic properties during metabolism. Investigations have shown that the site of their vascular action depends not only on the dose administered but on the chemical structure of the particular substance and thereby have furnished a pharmacologic basis for the occurrence of arteriosclerotic lesions in the vessels of restricted provinces (Hochrein and Keller; Chen and Meek; Sturm, Geitz and Kempfle). These substances have a widespread use as vasoconstricting agents in the treatment of head colds, bronchial asthma, hay fever, fatigue, obesity, hyperthyroidism, alcoholism, hypotension and migraine. With proper medication amphetamine and ephedrine elicit an increase in blood pressure which can be sustained for days or weeks (Ogden and Teather; Wand).

Tyrosine, which occupies a key position in the production of epinephrine, melanin, thyroxin and pitressin and is an integral part of the structure of many enzymes and proteins of immunity, has been related recently to the mechanism operative in the production of the hypertension that occurs in rats and cats after they have been fed excessive amounts of tyrosine or after they have received injections of this amino acid (Martin; Malorny and Orzechowski). Subsequent studies of rats which received a diet containing 11.17 parts of tyrosine showed intimal proliferation in the meningeal vessels and swelling and hyalinization of the walls of cerebral, renal, cardiac and pulmonary arterioles (Hueper and Martin). It is noteworthy that in ochronosis, caused by an abnormality of the tyrosine metabolism and elicited in its exogenous form by chronic phenol poisoning (Smith), arteriosclerotic lesions are frequently observed (Fishberg; Jantke; Poulsen).

Tyramine, which is derived from tyrosine by decarboxylation, has been described as the pressor factor of the ischemic kidney and has been connected with the causation of pale hypertension (Holtz and Heise; Heinsen and Wolf; Wolf and Heinsen; Bing; Oster and Sorkin; Prinzmetal, Lewis and Lee). It was claimed that l-tyrosine is not deaminated in the diseased ischemic kidney, but only decarboxylated, forming oxytyramine (Holtz; Zipf and Gebauer). While these contentions have not been wholly confirmed, tyramine is a powerful vasopressor amine (Robbers; Myer and Eckers; Enger and Lampas). Tyramine is not a pure sympathetotonic agent since in addition to stimulating the sympathetic nerve endings it acts directly on the smooth muscle and increases thereby the peripheral vascular tonus. Its pressor action

is more prolonged than that of epinephrine (Wolf and Ludolph).

When administered to rabbits (Harvey) and to dogs (Paunz; Enger and Lampas) tyramine produced medial degeneration and calcification of the aorta and of the renal vessels. Heinlein, Rühl and Duff, Hamilton and Magner reported sclerosing intimal changes and hyalinizing medial lesions in the coronary, cerebral and renal arteries and arterioles in rabbits given repeated injections of this substance.

Loewi and Meyer produced aortic degenerations in rabbits by the introduction of several synthetic substances chemically related to epinephrine (aminoacetypyrocatechol; methylaminoacetypyrocatechol; ethylaminoacetypyrocatechol). The methyl derivative elicited these lesions not only after intravenous but even after subcutaneous injection. Repeated injections of pyrocatechin, which has no pressor effect, had practically a negative result as to arterial lesions in rabbits (Loeb and Githens). Chen and co-workers recorded the development of disseminated sclerotic foci and hypertrophic and hyperplastic changes in the small arteries and arterioles of rabbits receiving large doses of ephedrine. The absence of fatty deposits in these lesions was especially mentioned. Ehrich, Lewy and Krumbhaar injected amphetamine into monkeys daily for a period of about six months and noted chronic vascular lesions in the brain, the spleen and the kidneys such as occur in mild hypertension. The brains of dogs which had received the drug orally for such a period exhibited hyaline degeneration of the cerebral arterioles and perivascular round cell infiltration, whereas the arterioles of the kidneys and the spleen had thickened but not sclerotic walls. Rühl saw in 1 of 3 rabbits given ephedrine intravenously (phenylmethylaminohydroxypropane) thickening of myocardial arteries and renal arteriolar changes similar to those found in lead-induced nephrosclerosis.

Mention may be made in this connection of the occasional occurrence of marked hypertension in persons with melanosarcomatosis even when the adrenal glands are completely destroyed by tumor tissue (Strumia). Davidsohn obtained an epinephrine-like action from an extract of a bilateral tumor diagnosed as adrenal melanoma. Tuczek stated that such tumors originate from the adrenal medulla. However, Goldzieher, who commented on adrenal melanoma, as well as Jäger, who studied melanosarcomatosis in white horses, noted that there were no arterial sclerotic or medial lesions or myocardial scars suggesting an increased epinephrine content of the blood.

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**Psychic Strain.**—It is generally agreed that the vascular reactions accompanying nervous tension, anxious states, emotional episodes and prolonged psychic strain are associated with increased blood pressure and fluctuations in the amount of epinephrine released from the adrenal glands (Master, Dack and Jaffe; Brooks; Guttman and Mayer-Gross; Ayman and Pratt; Alexander; Weiss; Stieglitz; von Diringshofen and Belonoschkin). In view of the well established arteriosclerogenic action of this hormone, efforts have been made to correlate the incidence and the localization of arteriosclerotic lesions observed in workers in the various occupations with occupational factors causing frequent and prolonged excessive psychic strain and thereby elevated output of epinephrine with the ensuing vascular spasm (Hall; Pawinski; Weiss). However, the psychic genesis of arteriosclerosis has remained uncertain (Goldscheider) in spite of extensive statistical studies undertaken in this direction. Pedley stated that in North America the facts are meager but suggest a greater incidence of disease of the coronary arteries among higher economic groups. The most vulnerable occupational group, according to the statistics of the Metropolitan Life Insurance Company, is that of physicians and surgeons, who show a mortality rate from disease of the coronary arteries six times that of general laborers. Lawyers, clergymen, insurance officials, clerks, all show relatively high mortality from disease of the coronary arteries, while the lowest mortality occurs among agricultural laborers and horticultural workers. Smith made similar observations in regard to the incidence of coronary arteriosclerosis among the members of different occupations when examining 307 physicians, 300 bankers, 304 lawyers, 306 pastors, 306 laborers and 308 farmers. The medical group had coronary arteriosclerosis in 10.7 per cent, the banking group in 5.3, the ministerial and legal groups in 4.6, the labor group in 2.6 and the agricultural group in 2.5 per cent. Hedley also concluded that disease of the coronary arteries is highest among business and professional people in the age group 55 to 64, according to evidence obtained from an analysis of deaths in the Philadelphia area in the period from 1933 to 1937. Smith concluded from this evidence that coronary arteriosclerosis as a result of occupational injury is less frequent in manual laborers than in brain workers. Similar studies culminated in opposite conclusions, neither physicians nor business executives being found especially predis-

posed to acquire disease of the coronary arteries (Gosse; Levy, Bruenn and Kurtz; Master, Dack and Jaffe; Hyman). Grotel, Bykhovskaya, Pavlova, Pokhodilova and Shor, on the other hand, confirmed the reports of Smith and Pedley; they found that psychic trauma was absent in 32.5 per cent of their cases of mild coronary arteriosclerosis, whereas it was absent in only 17.3 per cent of their cases of severe involvement. Shocking or sudden psychic trauma and intensive intellectual labor were demonstrated predominantly in the group with grave sclerosis of the coronary arteries, whereas chronic, protracted trauma was more frequent in the group with sclerosis of the cerebral arteries. Schwartz and Harvey furnished additional evidence supporting these conclusions from their studies of the incidence of disease of the coronary arteries among persons working in the financial area of New York. They observed that the incidence of complaints attributable to such disease fluctuated with the activity of the stock market ticker, but mentioned that 42 per cent of their patients from this district with such complaints were heavy smokers. Other investigators (Herz; Dobuff, Peneff and Wittkova; Bähr; Stephan) also noted that occupational nervous excitement plays a definite role in the genesis of diseases of the coronary arteries. The observations of Mönckeberg and Kohlhaas as to the incidence of coronary arteriosclerosis in young soldiers during World War I point in this direction (Groedel; Cramer). Cobb and Blain, as well as Fahr, noted that there exists much clinical evidence that people living under emotional stress show cerebral arteriosclerosis at an unusually early age.

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*Adrenal Cortical Hormone.*—A certain fraction of the hormone of the adrenal cortex or its synthetic substitute, desoxycorticosterone, exerts a definite vasopressor action (Kendall; Kepler and Willson; Kepler and Keating; Grollman, Harrison and Williams; Loeb; Ferrebee, Ragan, Atchley, and Loeb; McCullagh and Ryan; Rodbard and Freed). Moreover, numerous observations indicate that a causal relation exists between diffuse or nodular hyperplasia and adenoma of the adrenal cortex and hypertension (von Lucadou; Sarason; Kepler and Keating; Mainzer; Rinehart, Williams and Cappeller; Hantschmann; Hoffmeyer; Neuhaus; Cahill, Melicow and Darby; Moehlig and Bates), especially as such cortical enlargements also accompany the hypertension present in cases of basophilic adenoma of the pituitary gland (Cushing's disease) and in pregnancy (Calder and Porro; McMahon, Close and Hass; Kessel; Raab). An appreciable number of the patients with such cortical enlargements, many of them infants or young adults, show arteriosclerosis and arteriolosclerosis, including nephrosclerosis. Inasmuch as this condition is usually accompanied by plethora, osteoporosis, polycythemia and an increase in blood cholesterol the lesions of the arteries often exhibit not only sclerosing intimal and medial changes but changes of atheromatous lipoidal nature, as well as changes of a calcinotic medial type (Hoffmeyer; Raab; Moltschanoff and Davidowsky; Cushing; Kessel; McMahon, Close and Hass).

Supporting the causal relationship between the hypertension induced by the hormone of the adrenal cortex and arteriosclerosis are the observations of workers who succeeded in eliciting arteriosclerotic lesions in animals by repeated implantations of adrenal cortex (Leriche and Froelich; Hornowski; Maggi and Mazzocchi). Additional evidence in this respect is provided by the recent experiments of Selye and of Selye and Stone, who were able to produce in chicks and rats nephrosclerotic changes with fibromuscular thickenings in the medium-sized arterioles by repeated injections of overdoses of desoxycorticosterone acetate.

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*Pituitary Hormones.*—Proliferation of the basophilic cells of the anterior lobe of the hypophysis either in the form of adenoma or as a more diffuse growth invading also the posterior lobe has been found to be frequently associated with vascular hypertension. Cushing advanced the theory that in hypertension (eclampsia, essential hypertonia, arteriosclerosis, basophilic adenoma) the invasion of the posterior lobe by basophilic cells from the intermediary zone is an expression of hypersecretion of the vasopressor hormone of the posterior lobe. Such changes had been reported previously in connection with nephrosclerosis, uremia and renal amyloidosis (Berblinger; Kraus; Hoeppli; Kraus and Traube; Erdheim, and others), as well as later (Baumgartner; Marciano; Houssay; Jores, Plant and others). However, these contentions have not remained undisputed, as similar basophilic infiltrations of the posterior lobe were seen in conditions not associated with hypertension; on the other hand, they were found lacking in cases of

hypertension (Scriba; Spark; Leary and Zimmerman; Ahlström). Additional controversy arose in regard to the functional significance of such basophilic hyperplasia in relation to hypertension. Houssay considered three possibilities: hypertension may be due (1) to a specific secretion of the basophilic cells; (2) to stimulation of the pressor secretion of the posterior lobe; (3) to an action through some other gland. There is to be added a fourth possibility, that simultaneous hyperplastic changes in the adrenal cortex, which frequently coexist with basophilic adenoma as well as with other hypertensive conditions, furnish the pressor substance. Jores concluded from his hormonal studies that essential hypertension is elicited by the corticotropic and adrenotropic hormones of the anterior lobe of the hypophysis. Albright, Parsons and Bloomberg maintained that Cushing's syndrome has origin in hyperactivity of the adrenal cortex. Ruggieri stated in regard to basophil adenoma either hypertension is secondary to cerebral arteriosclerosis or hypertension and arteriosclerosis are unrelated. He apparently reached this conclusion because he found arteriosclerotic changes in pituitary dwarfism, in which the blood pressure is low. No definite decision in this matter is possible from the evidence available at this time.

Ruggieri noted that extensive vascular changes were present in 31 cases of basophilic adenoma studied, although only 3 of the patients were over 40 (Anderson; Reichmann; Mooser; Oppenheimer and Fishberg; Weber; Bauer; Cushing; Bishop and Close; Rutishauser; Sahn; Craig and Cran; Russell; Ruggieri and co-workers). To this number must be added the cases of: Raab; Calder and Porro; McMahon, Close and Hass; McMahon; Baumgartner. Irrespective of the alleged causal significance of the basophil cellular proliferations in regard to hypertension of various genesis, there thus remains the fact that the hypertension associated with basophilic adenoma is always combined with severe arteriosclerotic changes affecting the large and small vessels of numerous organs (Carmalt-Jones).

Whereas there is no agreement as to whether or not the hypertension and consequently the arteriosclerosis connected with basophilic adenoma are caused by an overproduction of the pressor substance of the posterior lobe of the pituitary gland (pitressin), which constricts the peripheral arterioles, Moehlig and Osius succeeded in eliciting aortic arteriosclerosis in rabbits by injecting an extract of the posterior lobe. Mention may be made also of an observation of Griffith and associates, who caused the development of persistent hypertension in

rats through repeated injections of pitressin. Holsclaw and Booth reported the occurrence of gangrene of the hands and feet in a baby who had received an overdose of an extract of the posterior lobe and who thereafter had cold, purplish extremities with areas of demarcation. Vasospastic episodes elicited by the intravenous introduction of pitressin caused ulcers of the gastric mucosa in dogs and spotty cerebral degeneration associated with endothelial proliferation and hyalinized thrombi in the contracted small vessels in these tissues (Nedzel; Berg), attesting that an anoxemic mechanism is active in the production of the parenchymatous as well as the vascular lesions.

It is obvious from these data that the pressor hormone of the posterior lobe of the pituitary gland can produce degenerative and sclerosing arterial lesions, but there does not exist any valid evidence indicating that it plays a significant part in the general genesis of hypertension and thus of arteriosclerosis (Grollman, Harrison and Williams; Hoyle; Page).

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*Parathyroid Hormone.*—Hypersecretion of the parathyroid hormone or parenteral introduction of this substance (Collip) results not only in hypercalcemia and hyperphosphatemia, but in bradycardia and increased vascular tonus (Berency). Tachycardia and vascular hypotonia develop only when, through the action of toxic amounts of parathyroid hormone, anatomic degenerative changes have occurred in the myocardium and the tissues of the vascular walls. The functional effects of parathyroid hormone thus closely resemble those exerted by digitalis glucosides (Pohle; Schretzenmayr; Billigheimer; Zondek).

Hyperparathyroidism is either of primary nature and then caused by adenomatous hyperplasia of the parathyroid gland (Albright, Aub and Bauer; Assmann; Kahlau; Hoffheinz; Soffer and Cohn; Arnold; Siebenmann; Dawson and Struthers; Paul; Bergstrand; Barr and Bulger; Peneke; Johnson; Quick and Hunsberger; Baird, Cope and Bloomberg; Mayer, and others) or of secondary character accompanying chronic renal diseases, such as chronic glomerulonephritis, polycystic kidney and renal rickets (Pappenheimer and Wilens; Danis and Rossen; Nelson; Magnus and Scott; Bergstrand; Kluge; Gutman, Swenson and Parsons; Ohntrup; Herxheimer; Hubbarth and Wentworth; MacCallum; Gilman and Martin; Eger; Highman and Hamilton; Schellack; Rutishauser; Anderson; Castleman and Mallory; Radnay; Jarreitt, Peters and Pappenheimer; Pappenheimer; Koopman; Vines; Smyth and Goldman; Lightwood; Smyth and Goldman; Tomaszewski; Surbek; Oppenheimer; Bryant and White; Forrer; Bernhard; Jamison and Hauser; Benda; Herzog; Hesse and Zinserling; Baggenstoss and Keith; Bolman; Brown and Ginsburg; Anderson). Inasmuch as the hormone of the parathyroid glands favors acidotic metabolism and therefore mobilization of calcium

from the bones, hyperparathyroidism is characterized, on one hand, by osteoporosis and osteitis fibrosa and on the other, by metastatic calcification of degenerated and necrotic tissue of various organs, especially those which release acid values (lung, myocardium, thyroid, gastric mucosa, kidney, arterial walls) (Wells). It is claimed, moreover, that cutaneous calcinosis with scleroderma (Leriche) as well as cerebral calcifications are related to functional disturbances of the parathyroid gland (Ostertag; Albright; Eaton and Haines; Bassoe). Erythropenia and leukopenia, found with hyperparathyroidism, on the other hand, are attributable to the progressive fibrosis of the bone marrow.

The degenerative arterial changes consistently associated with marked hypersecretion of the parathyroid hormone are a result of the combined influence of the vasculotonic functional effects and the hypercalcemic metabolic disturbances and represent, together with the organic calcifications, a reaction typical for such a syndrome. It is significant that the arterial lesions observed with hyperparathyroidism occur in persons of all ages but particularly in young children and young adults. Identical vascular changes have been elicited in experimental animals (dogs, rats, mice) by parenteral injections of parathyroid extract (Hueper; Learner; Hoff and Homann; Cantarow, Stewart and Hansel; Jaffe; Moore; Chown, Lee, Teal and Currie; Homann; von Brand, Holtz and Putschar). Hyperparathyroidism secondary to renal disease has been reproduced in rats and dogs by excision of a portion of one kidney and removal of the other (Highman and Hamilton; Pappenheimer). While the medium-sized and small arteries are mainly affected, in severe poisoning with parathyroid hormone both the elastic (aorta, pulmonary artery) and the muscular arteries (cerebral, coronary, pulmonary, renal, femoral, osseous) show degenerative lesions.

The histologic vascular changes consist of primary necroses of the media, which may develop within one to two days after the administration of massive doses of parathyroid extract and which become rapidly and extensively calcified under the influence of the existing hypercalcemia, as calcium is readily precipitated in the alkaline necrotic tissue. The mediocalcinosis may convert smaller arteries into thick calcified rings. The calcification in the media of the large arteries is usually only focal. If the hyperparathyroidism is of chronic and rather mild type, the media of the medium-sized and small vessels becomes hyaline and shows only spotty calcification, while the intima undergoes fibrous thickening.

These vascular changes lead to severe functional and anatomic disturbances in the affected organs (necroses in the brain, the myocardium, the kidneys, the gastric mucosa, the liver). Assmann reported the occurrence even of symmetric gangrene of both large toes in a boy 16 years old, who was suffering from hyperparathyroidism with osteitis fibrosa.

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**Vitamin D.**—Vitamin D, synthetic or natural (contained in cod liver oil or other oils, such as viosterol), is used over long periods and sometimes in massive doses in the treatment of rickets,

arthritis, tetany, radium poisoning and various allergic states (Tumulty and Howard); infrequently such treatment produces toxic symptoms. The administration of toxic doses of vitamin D to dogs and cats causes hypertension, according to some (Doxiades; Appelrot; Heymans; Goormaghtigh and Handovsky). This has been disputed, however, by others (Heubner; Strisower; Holtz; Briskin, Stokes, Reed and Mrazek). Briskin and co-workers used rats and suggested that the alleged hypertensive action of vitamin D seen in dogs might be attributable to renal arteriosclerosis (Heymans), as hypotension developed in their rats. Doxiades, on the other hand, limited the hypertensive effect of vitamin D to young animals. The reason for this discrepancy may be sought more likely in the marked differences in susceptibility to this agent of the various species (Taylor, Weld, Branion and Kay); dogs and human beings are most susceptible, while rats can withstand enormous doses of the vitamin. The type of diet given, in addition to considerable individual differences in susceptibility, represents another important factor influencing the degree of toxicity and thus the pharmacologic action of the vitamin (Oppel). Severe myocardial damage resulting from vitamin D poisoning may cause hypotension.

It is generally agreed that the toxic functional and anatomic effects elicited by excessive doses of vitamin D are related to the ensuing hypercalcemia and hyperphosphatemia. An elevation in serum cholesterol has been observed in cats and rabbits (Hermann; Handovsky; Behrend and Berberich; Haendel and Malet) and in man (Lasch). The fluctuation in man, however, was not marked; it remained within the normal range.

The arterionecrotic action of hypervitaminosis D has been demonstrated in studies of a limited number of human subjects and in extensive experimental investigations on various species (monkeys, dogs, cats, rabbits, guinea pigs, rats, mice and chickens). The arterial and arteriolar lesions in their extent, anatomic character and organic distribution, as well as in their causative mechanism, are identical with those associated with parathyroid hormone poisoning.

While the great majority of investigators agree that the arterial and metastatic organic calcifications are of secondary nature, i. e., follow the primary degeneration and necrosis of the tissues brought about by circulatory disturbances, it has been maintained that the calcifications occur in the absence of degenerative changes (Ham, Ham and Lewis). These observers stated that the media of the coronary arteries of hypervitaminotic rats calcifies and that this is followed by

proliferation of cells in the intima. It is a well known fact that the histologic demonstration of cellular degeneration by the ordinary staining methods is entirely inadequate for the visualization of early cellular regressive changes. Hueper showed that in rats poisoned with vitamin D there occurs in the myocardium a focal accumulation of calcium, which is clearly demonstrable in ashed sections, and that the sections stained with hematoxylin and eosin do not reveal any cellular abnormalities in some of these foci. Inasmuch as the accumulation of calcium in the cells is a definite sign of necrobiosis, it is obvious that severe functional and metabolic regressive aberrations may be present in the tissue long before positive staining reactions for calcium are obtained.

It may be pointed out, moreover, that numerous observations have shown that degenerative vascular changes (loosening and swelling, glassy vesicular cells, disintegration of cells and fibrils and hyalinization of the media, as well as fibrous thickening of the intima) without calcifications are present whenever low toxic doses of vitamin D are used. These changes contrast with the extensive medial calcifications and necroses in the aorta and the coronary arteries seen in response to the administration of massive doses of vitamin D. Goormaghtigh and Handovsky brought out these differences by using graduated doses in their experiments. If these authors, as well as Wolbach and Bessey, conclude from this evidence that there is a specific toxic action other than the effect of vitamin D on the vascular wall through the calcium and phosphorus metabolism, they overlook the fact that the existence of similar morphologic differences of the arterial lesions which develop in response to large and small doses of vasotonic agents with markedly different chemical character militates strongly against such an interpretation.

Levaditi and LiYuan, as well as von Brand, Holtz and Putschar, did not see any renal calcification in rhesus monkeys with hypervitaminosis D. Cowdry and Scott obtained in monkeys intimal thickenings with rarefied cells but no medial calcinosis. Hypertrophy of the renal arterioles and medial calcinosis of the afferent arterioles (arteriolonecrosis) were seen in dogs subjected to hypervitaminosis D (Heymans; Appelrot; Goormaghtigh and Handovsky; Hess, Benjamin and Gross). While Goormaghtigh and Handovsky found gross aortic changes in dogs only after thyroidectomy, Palaske observed focal calcification involving the entire length of the aortic media in a 6 month old dog after the administration of high doses

of viosterol, and Kreitmair and Hintzelmann noted focal calcification of renal arteries.

Extensive mediocalcinosis involving both large and small arteries is commonly seen as a result of hypervitaminosis D in rabbits (Palaske; Schiff; Vanderveer; Billig; Schmidtman; Pfeleiderer; Harrison; Spies; Hüchel and Wenzel; Simmonet and Tanret; Junck; Huebschmann; Spies and Glover; Heubner; Wenzel; Laas; Varela, Collazo, Moreau and Rubino; Strisower; Dietrich; Falk; Pfannenstiel; Kreitmair and Hintzelmann; Haendel and Malet; Kreitmair and Moll).

Similarly extensive mediocalcinosis of the arteries occurs in cats after vitamin D poisoning (Kreitmair and Hintzelmann; Falk; Tammann; Reed, Dillman, Thacker and Klein; Berberich) and in mice (Kreitmair and Hintzelmann; Vara-Lopez), while guinea pigs (Kreitmair and Hintzelmann; Vara-Lopez) show only minor lesions.

The rat, which has been used most often in the studies of hypervitaminosis D, presents widespread and severe medial calcinosis in large and small arteries and arterioles, followed by fibrous intimal thickenings as compensatory and reparatory phenomena (Kreitmair and Hintzelmann; Rabl; Reyher and Walkhoff; Schmidtman; Selye; Herzenberg; Shohl, Goldblatt and Brown; Demole and Fromherz; Ham and Portuondo; Ham; Ham and Lewis; Reed, Dillman, Thacker and Klein; Oppen; Sweeney and Smith; Harris, Ross and Bunker; von Brand, Holtz and Putschar; Wenzel; Varela, Collazo, Moreau and Rubino).

Observations in man in regard to the arterionecrotic and arteriosclerotic action of hypervitaminosis D are relatively scanty. Some of the reported cases are of accidental nature; others are of experimental character. Postmortem observations have been made in several cases of suspected therapeutic vitamin D poisoning with arterial calcifications (Schmidtman; Gerlach; Malmberg; Eisler; Thomasen; Lippincott; Karelitz and Kolomozyeff; possibly Lightwood; possibly Brown and Richter). In a case recorded by Putschar and in a case by Thatcher renal calcifications occurred without involvement of the renal vessels. Schallock, in a study of 10 babies who had received between 7.5 and 15 mg. of vitamin D<sub>2</sub> or vitamin D<sub>3</sub>, was unable to confirm the positive findings of Schmidtman in babies after vitamin D medication. Vollmer, as well as Spies and Hanzal, administered lethal doses of vitamin D to a total of 6 children nearing the end of fatal diseases (miliary tuberculosis, leukemia, carcinoma) and were unable to demonstrate histologically any organic or vascular calcifications in the postmortem material. It

is doubtful whether reliable and definite conclusions as to the reactivity of man to vitamin D can be drawn from these observations since the experimental periods of six to twenty-five days may not have been sufficiently long for the development of late arterial effects such as those described by Schmidtman as occurring in rabbits after the administration of sublethal doses of vitamin D.

The findings regarding the successful transmission of vascular vitamin D injury from the mother to the offspring in rabbits (Nicole; Schiff; Laas; Schmidtman; Junck; Herzenberg; Pfeleiderer; Collazo, Rubino and Varela; Selye; Collazo) are probably significant, although Jeckeln failed to confirm these observations in rabbits, guinea pigs and rats.

Brief mention may be made finally of a claim of Simmonet and Tanret that the administration of potassium iodide inhibits the development of arterial calcinosis in vitamin D-poisoned rabbits. Thoenes, as well as Gross-Selbeck, claimed to have succeeded in offsetting the symptoms of hypervitaminosis D in rats by the administration of large amounts of vitamin A. Sweeney and Smith saw an aggravation of the vitamin D arteriocalcinosis in rats after the administration of parathyroid hormone. Schmidtman reported a similar accentuating action from calcium medication.

Schmidtman's experiments showed that cessation of the administration of vitamin D does not cause an arrest in the progressive development of the arterial lesions. Death may occur suddenly after a symptom-free interval, and the animals may then exhibit severe mediocalcinosis. Schiff arrived at the same conclusion and noted that there was no evidence concerning any repair or reversibility of the lesions once produced.

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**Ultraviolet Rays.**—Exposure to ultraviolet rays such as those contained in the solar spectrum and those produced by ultraviolet ray lamps elicits in the skin of man and animals photochemical reactions involving the production of vitamin D, the generation of melanin from a precursor of epinephrine, tyrosine, the destruction of vitamin C and the release of histamine. While histamine is a product of an acute actinic reaction, the development of appreciable amounts of viosterol and of melanin under such circumstances is a more prolonged process.

The gradual drop in blood pressure which follows solarization and lasts for several days is caused by peripheral vasodilatation, the action of vasodepressing proteolytic substances and a drop in blood tyrosine indicating a deficiency of epinephrine. With repeated exposure to ultraviolet rays and increased pigmentation, the blood pres-

sure rises and runs parallel to the degree of melanosis (Rothmann), while the blood tyrosine may remain low. Blood calcium is apt to be increased. Dodds, Robertson and Roche, studying children exposed to solar radiation for several months, found no evidence of hypervitaminosis D as the result of this treatment. The same conclusion was reached by Blum and Lippincott while investigating mice exposed to ultraviolet rays in amounts suitable for the production of actinic cancer.

Zurukzoglu and Gordonoff reported that in rabbits fed nonirradiated ergosterol and subsequently exposed to ultraviolet rays or intense solar rays mild signs of arteriosclerosis developed, such as thickening and lipoidosis of the intima and loosening of the media. Hueper, working with haired and hairless rats, which were exposed to carcinogenic doses of ultraviolet rays, observed an excessive incidence of hyaline and calcified medial lesions in the aorta and the coronary, pulmonary, pancreatic, renal, adrenal and testicular arteries, which increased in frequency, extent and severity with the duration of the treatment. The frequent coexistence of neoplastic and arteriosclerotic and arterio-calcinotic lesions in the irradiated rats suggested to Hueper that both manifestations were the results of an excessive exposure to the actinic energy.

#### *Ultraviolet Rays:*

Blum, H. F., and Lippincott, S. W.: *J. Nat. Cancer Inst.* **2**:623, 1942.

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**Calcium Salts and Acidosis.**—In addition to the hypercalcemia caused by parathyroid hormone poisoning and that due to hypervitaminosis D there is the hypercalcemia which results from excessive intake of calcium salts or from acidosis-producing chemicals mobilizing the calcium in the osseous structures or from extensive destruction of bony tissue or osteoporosis, such as occurs with cancers, multiple myeloma, endocrine disturbances of pregnancy, athyreosis and nephrosclerosis. Sequelae of such imbalances of the calcium metabolism are calcifications of the arterial walls and of certain organs similar to those found with the hypercalcemias of parathyroid hormone and vitamin D origin.

Katase, who injected solutions of several calcium salts (calcium chloride, calcium carbonate, tribasic calcium phosphate) into rabbits and guinea pigs intraperitoneally, intravenously and subcutaneously obtained medial calcifications in

the basal arteries of the brain and in the aorta in addition to calcified deposits in the brain around intact capillaries. Similar experiments with identical results were reported by Tanaka. Rabl observed extensive medial calcifications in the aorta and large arteries of mice which received for as long as forty-five days a diet rich in calcium which was made alternately acid with phosphoric acid for two days and alkaline with sodium acetate for the following two days. Dreyfuss repeated Rabl's experiment and noted arterial medial calcifications not only in the acid-alkaline group but to the same degree also in the group whose diet was kept uniformly acid. There were also calcifications in the intima. Kleinmann, using mice, fed and injected calcium salts (calcium chloride, calcium lactate, calcium phosphate), to which basic phosphate, acid phosphate and ammonium chloride were added for alkalinizing or acidifying effects. Calcifications occurred only in acid animals, not in those receiving basic phosphate additions. McJunkin, Tweedy and Mencky obtained necroses and calcifications in the aortic media of the rat after bilateral nephrectomy and after injection of calcium gluconate.

Following the observation of Fazekas that oral administration of toxic doses of ammonium hydroxide and sodium hydroxide to rabbits elicits acidosis, von Baló repeated this experiment by giving rabbits ammonium hydroxide for a period of one to seventeen months. In spite of marked lipemia there were mainly medial necroses in the aortas of these animals, affecting particularly the thoracic part. Similar changes were seen only occasionally in the abdominal part of the aorta and in other arteries. These lesions started with a degeneration of muscle cells, leaving the elastic membranes intact, though these later exhibited granular disintegration. In areas in which the medial necroses did not readily calcify the overlying intima became thickened, while early calcification of these lesions apparently prevented the reactive intimal thickening. The changes resemble those of epinephrine-induced sclerosis. Von Baló noted that as acidosis also occurs with diabetes mellitus, nephritis and lead poisoning, this metabolic disturbance may play an important role in the etiology of human arteriosclerosis. It may be mentioned that ammonium hydroxide exerts an acidotic effect only after oral administration; it is converted in the stomach into ammonium chloride, which is resorbed and responsible for the ensuing acidosis (Alwall and Geiger). Investigations of Haldane, Linder, Hilton and Fraser have shown that ammonium chloride acidosis produces a prolonged reduction in the oxygen capacity of the blood in man,

resulting in damaging action on the vascular endothelium and thus in accentuation of the vasculotonic anoxic injury of the vascular wall caused by the hypercalcemia.

Hoelzer compared the mechanism operative in the production of bony changes and the diffuse and generalized mediocalcinosis of the large and particularly the small peripheral arteries in a girl 2.7 years old, who was suffering from glomerulonephritis, with that active in similar osseous and arterial manifestations in hypervitaminosis D. The etiologic relations of chronic renal diseases to arterial mediocalcinosis were discussed previously in connection with the secondary hyperparathyroidism seen under such circumstances. Bony changes may be absent in some of these cases (chalky gout) (Schmidt; Stumpf). In other cases of chalky gout even renal lesions may be absent, but there often is a vasospastic component of the Raynaud type affecting the hands or the feet (Westerlund; Rosenberg; Costello), which is frequently associated with scleroderma and sclerodactylia (in about 33 per cent of 71 cases reported by Steinitz). Similar arterial and organic metastatic calcifications were observed by Grayzel and Lederer in a girl aged 13 with leukemic myelosis in the presence of severe hypercalcemia, as well as in a pregnant woman aged 25.

While Weiss and Minot in their treatise on nutrition in relation to arteriosclerosis did not favor the existence of any causal connections between these two factors in man, and while this position was maintained by Weiss and Wilkins up to 1937 with only minor concessions concerning the occasional occurrence of such interrelations, there is available now sufficient and reliable evidence supporting the presence of causal relations between nutrition and arteriosclerosis in experimental animals. Kollath, as well as Kollath and Giesecke, studying rats kept on a diet deficient in all vitamins except vitamin B<sub>1</sub>, observed nephrosclerosis and calcifications in the pulmonary arteries. These authors mentioned that the diet was related to the one by which Katase elicited arterial mediocalcinosis and produced nutritional disturbances resembling those of pellagra in rabbits. Calder, who fed rats a diet deficient in the heat-stable fraction of the vitamin B complex, noted the development of hypertension together with renal lesions such as those seen in nephrosclerosis. Some of the large interlobular arteries showed thickened walls and narrowed lumens. Similar arteriosclerotic lesions were seen in rats which received yeast ad libitum or liver extract. Rats which were fed only small amounts of yeast exhibited numerous arterioles

with degenerated walls and subendothelial hyalinosis (arteriolosclerosis). Complete obliteration of the lumens was occasionally seen. The observations of McCay on the occurrence of severe aortic sclerosis and calcinosis in rats kept on a diet apparently deficient in vitamins supplies additional evidence in this respect. In this connection mention may be made of the statement of Rossi concerning the development of sclerosis of the cerebral arteries in connection with pellagra, and to that of Babes, Babes and Babes in regard to the frequency of sclerosis of the large vessels in persons suffering from this avitaminosis. Winkelman also noted degenerative changes in the cerebral vessels, particularly in the small vessels, of 2 persons with pellagra.

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*Digitalis Glucosides and Strophanthin.*—Certain glucosides contained in preparations of digitalis, strophanthin and adonidin, have a distinct vasopressor effect (Blickensdorfer and McGuigan; Klotz; Saltykow; Otto). When given in excessive doses they produce marked hypertension, bradycardia, attacks of angina pectoris and a hard, wiry pulse and in the case of overdigitalization may elicit by spasm of the retinal artery even transitory ischemic blindness similar to that seen in lead poisoning. Preparations of digitalis have been used recently extensively in fraudulent attempts to obtain compensation under life insurance contracts by simulating cardiac disorders (Hedley).

In rabbits the intravenous injection of various preparations of digitalis (digitalin, digalen, digitaline kativelle, digitoxin), (Fischer; Orlowsky; Klotz; Morelli; Kon; Rühl) or of solution of strophanthin (Orlowsky) or solution of adonidin (Orlowsky; Weselkow; Otto) has been followed by the development of acute aortic medial necroses and calcifications identical with those observed after injections of epinephrine. Boveri failed to obtain arterial lesions in rabbits with strophanthin. Hueper and Ichniowski reported the presence of edema and hyaline degeneration of the coronary and renal arteries and arterioles in cats which received lethal or sublethal doses of digitalis glucosides intramuscularly.

*Digitalis Glucosides and Strophanthin:*

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Weselkow: Russk. Vrach **6**:82, 1907.

*Hydrastine and Hydrastinine.*—The alkaloids hydrastine and hydrastinine, which are prepared from *Hydrastis canadensis* and which are used in obstetrics for their uterus-contracting action, also exert a definite constrictory effect on the peripheral vessels when given in moderate doses and thereby increase the blood pressure, under slowing of the heart beat.

Orlowsky, as well as Benecke, injected these substances into the veins of rabbits repeatedly over periods of several months and observed

medionecrosis and calcinosis in the entire aorta in 61 to 91 per cent of the animals thus treated, thereby showing again that severe and repeated vasospastic episodes elicit primarily medionecrotic reactions.

*Hydrastine and Hydrastinine:*

Benecke, A.: Virchows Arch. f. path. Anat. **191**:226, 1908.

Orlowsky: Russk. Vrach **4**:1443, 1905; **6**:364, 1907.

*Ergot.*—Circulatory disturbances on the basis of poisoning with the alkaloid ergot or its various derivatives, such as ergotamine and ergotoxine, which are extracted from the fungus *Claviceps purpurea*, infecting various grains, particularly rye, have been known since ancient times (ignis sacer; ignis St. Antoni). The consumption of bread prepared from infected grain caused in former centuries a considerable number of extensive epidemics of ergotism often leading to gangrene of the extremities through vascular spasm and obliteration in the affected persons (Barger; Kaunitz; Krysinisky; Yater and Cahill; Gould, Price and Ginsberg; Davis). These epidemics affected mainly the inhabitants of rye bread-eating countries, such as Russia, Germany, France and England. The last great epidemic of ergotism was observed in Russia during the years 1926 to 1927, among the people inhabiting the district between Kasan and the Ural Mountains. A smaller epidemic, involving some 200 persons of Jewish origin who were consuming infected rye bread, was recorded in Manchester, England, in 1929. Ergot occurs commonly in the United States on rye, wheat grass, wild rye, Kentucky blue grass, Canada blue grass, redtop, timothy and rye grass and occasionally on wheat (Klein; Atanasoff; Stevens and Hall; Kohler and Holbert). The relative frequency of ergot infection in the United States is evident from the fact that in Connecticut in 1920 from 1 to 5 per cent of the heads of rye were found infected, while in Russia up to 20 per cent of the heads were infected, according to Atanasoff.

In more recent years cases of vasospastic gangrenous ergotism are usually of medicinal nature, resulting from the use of the ergot alkaloids, especially ergotamine tartrate, in obstetric practice and in the treatment of migraine, thyrotoxicosis, amenorrhea and herpes zoster (Ellerbroek; Yater and Cahill; Gould, Price and Ginsberg; von Storch; Velkoff and Ferguson; Smith and Eusterman; Speck; Platt). Von Storch in 1938 collected 42 cases of medicinal ergotism, in 21 of which the condition was of the gangrenous type and 8 of the patients died. Nielsen reported a case of ergotism (erythromelalgia) following an attempt to commit suicide with

ergotamine tartrate. It may be mentioned that there is some evidence that the convulsive form of ergotism may also be related to functional and anatomic circulatory disturbances elicited by ergot in the cerebral vessels (Ehrhardt; Tuczek; Pool and Nason), as ergotamine causes constriction of the cerebral vessels (Graham and Wolff; Lennox and Leonhardt).

The first symptoms of ergotism are coldness and numbness of extremities, sometimes combined with dull and burning pains or cramplike sensations in the calf, formication, itching and attacks of intense waves of heat or cold in the extremities, and, in ergotism of long standing, increased blood pressure (Morgan). Later on, the extremities become swollen and livid or red violet, with the formation of blisters, and finally turn black after pulsation in the arteries has ceased. The symptoms thus resemble in part those seen in Raynaud's disease and in part those associated with thromboangiitis obliterans. Children are more susceptible to ergotism than adults, and men are more frequently affected than women (von Storch; Kaunitz). It is noteworthy, however, that the patients with medicinal ergotism are predominantly women.

The spasm responsible for the recorded symptoms affects primarily the arterioles and the small arteries, although at times the larger arteries are also constricted to a greater degree (Yater and Cahill). Under the influence of these functional reactions edema and fibrous thickening develop with concentric or eccentric folding of the intima and hyaline degeneration and fibrosis of the media of the affected vessels, leading finally to complete obliteration, which may be hastened by the occurrence of thrombosis. Lymphocytic infiltration of the walls is usually but not always observed. The arteriolar changes are similar to the arterial ones. Constriction and thickening of the venous walls also occur but are in general less marked than the arterial changes (von Storch; Barger; Vinogradoff; Kaunitz; Yater and Cahill; Gould, Price and Ginsberg). The whole process resembles thromboangiitis obliterans. The symptomatic and anatomic resemblance between vasospastic gangrenous ergotism and other ischemic gangrenous conditions of the extremities caused Raynaud and Ehlers to suspect that chronic ergotism may be etiologically involved in the production of symmetric gangrene of the extremities (Raynaud's disease). Kaunitz voiced a similar opinion and pointed to the pathologic analogies to other diseases of this type, such as thromboangiitis obliterans, erythromelalgia, acrocyanosis, scleroderma, multiple neurotic gangrene and others. It is his belief

that chronic endemic ergotism resulting from the daily consumption of infected rye bread might occur in the guise of these vascular, vasomotor and trophic diseases. Among the arguments supporting this point of view he mentioned that thromboangiitis obliterans, as well as gangrenous ergotism, affects mainly men of younger age groups; that as the infection of rye by ergot is slight, only the most susceptible persons suffer from its effects; that, owing to individual idiosyncrasies, intoxication with ergot is manifested in different forms of vascular, vasomotor or trophic type and that for this reason the more susceptible male has the severe form, thromboangiitis obliterans, as an allergic reaction to ergot, while the female is affected by the milder form, Raynaud's disease. Klein expressed a similar opinion some years ago, asserting that various varieties of fungi may be etiologically related to such similar diseases as erythredema polyneuropathy (acrodynia), Raynaud's disease, erythromelalgia, thromboangiitis obliterans (Buerger's disease) and pellagra and that the variations in vasomotor reactions may be explained by the varieties of ergot constituents on various cereal fungi. It is obvious that these far reaching conclusions are in disagreement with other evidence covering the causes of the various vasospastic conditions, as such a syndrome may also ensue after poisoning with arsenic, lead or nicotine and after exposure to cold and to repeated and prolonged rapid vibratory injuries.

Similar gangrenous and endarteritic changes have been produced in the combs of roosters (Custer; Kaunitz; Lewis and Gelfand) and in the tails of rats (Loewe and Lenke; Rothlin; McGrath; Kopet and Dille) by daily repeated intramuscular or subcutaneous injections of ergotamine tartrate and other alkaloids of ergot. The endothelial obliterative proliferations affected mainly the small arteries and arterioles. Thrombosis was present in the larger arteries. The veins showed intimal proliferation and thrombosis and often thrombophlebitis. In rabbits the intravenous injection of ergot preparations resulted in the development of acute necroses and calcifications in the media of the aorta such as those obtained by the intravenous administration of epinephrine (Loeper; Thevenot; Kriloff). After *Secale cornutum* had been orally introduced into rabbits for periods of up to ten months by d'Amato, a few small yellow areas and small aneurysms developed in the arch of the aorta.

McGrath noted that female rats receiving injections of theelin in addition to ergotamine tartrate did not have gangrene of the tail, while all unprotected male and female animals showed

this response. From this observation he concluded that basically thromboangiitis obliterans is possibly a disturbance of endocrine origin and that the failure of the disease to manifest itself in women or its tendency to occur in such a mild form that it escapes clinical notice may be associated with a protective action of the estrogenic principle of the ovary. Ratschow and Klostermann confirmed McGrath's observations. Normal female rats treated with ergotamine tartrate were protected by estradiol benzoate but not by testosterone. In castrated male rats both estrogen and androgen prevented ergotamine gangrene, whereas castrated female rats responded to estrogen only. Suzman, Freed and Prag obtained protection against ergotamine tartrate in both female and male rats with an estrogen (estrone) when large doses were given. The protection was less marked in males than in females. In commenting on these observations Suzman, Freed and Prag pointed to a report of Friedlander, Silbert and Laskey, who assumed that the relative immunity of women to thromboangiitis obliterans is of endocrine ovarian nature.

Loewe and Lenke, on the other hand, could not substantiate these observations on the protective action of estrogens (estrone; alpha estradiol benzoate in oil). Similarly negative results were recorded by Krueger, Ludden and Wright.

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*S-Methylisothiouraea*.—Recent experiments of Hueper and Ichniowski in which a new vasoconstrictor agent exhibiting a vasoconstrictory action (Smirk) similar to but more prolonged than that of epinephrine was repeatedly administered to dogs, cats, rabbits and rats orally and intravenously over a long period produced in a few of the dogs areas of edematous and albuminoid swelling of the intima and hyaline foci in the outer part of the media of the aorta. Dogs, cats, rabbits and rats exposed to this agent, S-methylisothiouraea, exhibited not infrequently hyperplastic swelling and fibrous thickening of the intima of the pulmonary arteries. The arterial lesions were those characteristic of a prolonged moderate hypertonic action on certain parts of the vascular tree.

#### S-Methylisothiouraea:

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**Barium Chloride.**—A number of investigations (Boehm; Mickwitz; Schedel; Bary) have demonstrated that barium chloride is a powerful vasoconstricting agent. Miller, Klotz and Benecke repeatedly injected barium chloride solutions into the veins of rabbits and observed extensive medionecrosis of the aorta resembling that found in acute epinephrine-induced sclerosis. Miller noted that the intima was also involved in the degenerative lesions. The combination of spermine with barium chloride in various proportions and types of administration failed to prevent the development of the aortic degenerations (Benecke).

**Barium Chloride:**

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**Lead.**—Acute and chronic lead poisoning of occupational, accidental or environmental origin is still a relatively common disease among adults as well as among children. It has many unsuspected sources (Flury; Conway; McKhann; Nye; Störing; Bruce; McDonald and Kaplan; Lanza; Machle; Dreessen; Koelsch) and, doubtless, escapes detection not infrequently, especially in its chronic renal form. While it is generally agreed that many of the symptoms characterizing this intoxication are the results of local vaso-spastic reactions caused by lead, either by a direct action on the vascular wall or by an increase in blood calcium (Reinhart) or a stimulation of the production and liberation of epinephrine (Teleky; Muck; Baader; Chajes; Litzner; Schneemann; Seitz; Otto and Hahn), there still exists a great deal of controversy as to whether or not lead poisoning has etiologic relations to general hypertension and systemic arteriosclerosis. Since the literature on lead intoxication now includes more than six thousand publications, it is beyond the scope of this review to deal with the dispute in a detailed manner.

Direct observations of the retinal vessels have demonstrated that under certain conditions lead causes temporary vascular contractions. Evidently such transitory vasospasms when affecting the cerebral vessels are responsible for the epileptic attacks and transient amaurosis. When involving the coronary arteries they account for the attacks of angina pectoris not infrequently observed in chronic lead poisoning. When acting

on the arteries of the extremities they may produce symptoms like those of Raynaud's disease (Sümegi; Heuben and Rosenstein; Elschwig; Rambousek; Hilka; Peiper; Lewin; Hirschfeld). According to Teleky, as well as Goadby, pallor of the skin is characteristic of chronic lead intoxication. They attribute it to a spasm of the small cutaneous vessels. The observation is also definitely established that during certain stages of lead colic the blood pressure rises to hypertensive levels. There seems to be no serious disagreement on the point that hypotension prevails during attacks of acute lead poisoning (Teleky; Petroff; Gray and Greenfield; Machle). The behavior of the blood pressure in chronic lead poisoning, on the other hand, is a matter of much dispute. Many investigators (Panse; Mayers; Gerbis; Flury; Zangger; Vigdortschik, and others) have contended that blood pressure is increased after chronic exposure to lead, while numerous others (Teleky; Lasius; Pfeil; Lederer; Jones; Engel; Dreessen; Gray and Greenfield; Kephoe, and others) could not find any appreciable or significant difference in the incidence of hypertension in lead workers and in workers who do not deal with lead.

The confusion in this respect is evidently attributable to the fact that the blood pressure in chronic lead poisoning fluctuates during the different stages of the disease. Statistical studies which do not take this fact into account are therefore easily misleading. Koelsch pointed out that the blood pressure is usually increased during the early stages and that this is the result of a functional vascular spasm, while it often drops to even a hypotonic level during the intermediary stage (Engel; Tschelzowa; Wassermann) but may rise again later when persistent hypertension develops on the basis of anatomic vascular changes in the renal vessels associated with nephrosclerosis saturnina. Grünberg related these fluctuations in the tonus of the smooth musculature of the vessels and the intestine, varying from primary sympatheticotonia to secondary vagotonia, to degenerative changes in the sympathetic ganglions.

Depending on the attitudes of the individual investigator toward this question of hypertension in lead poisoning is a corresponding difference of opinion concerning the presence of etiologic relations between lead poisoning and the development of local or general arteriosclerosis. Koelsch, as well as Aub, thus maintained that lead does not cause atheromatosis or arteriosclerosis of the large arteries but may produce arteriolosclerosis in the kidneys and the brain. Flury considered even the lead genesis of renal arteriolosclerosis

as controversial and insecurely established because of its relation to arteriosclerosis, old age and alcoholism. Mayers found the incidence of arteriosclerosis among lead workers high but not higher than in other groups of similar economic level. In Italy, on the other hand, arteriosclerosis following occupational exposure to lead is compensable (Sanseverino). Teleky stated that the anatomic changes in the vascular system of old lead workers indicate a heightened tonus. Wright acknowledged the arteriosclerotic action of lead.

Much more agreement prevails concerning the lead causation of degenerative, hyaline, calcifying and fibrosing medial and endarteritic intimal lesions observed after chronic poisoning in the arteries and arterioles of the kidneys, the brain, and, to a lesser extent, the heart, the peripheral nerves, the extremities and the skin, i.e., in organs in which functional vascular or parenchymatous disturbances apparently precede the onset of anatomic arterial changes (Engel; Fischer-Wasels; Teleky; Lanza; Kionka; Wagner; Geppert).

Lead is accumulated in the renal cortex and in the media of the renal vessels and can be demonstrated there by (a) spodography, which reveals a black-brown lead sulfide in a white to grayish white ash (Tada), (b) various histochemical methods (Kockel; Iwahashi; Timm; Henriques and Okkels), (c) the experimental use of radioactive isotopes, (d) photographic methods (Behrens and Anton) or (e) dark field examination (Rauh; Timm). The development of nephrosclerosis on the basis of chronic exposure to small amounts of lead exhibits, according to Volhard, the following sequence of events: spasm of intrarenal vessels, obliterating endarteritis with facultative elastosis, secondary nephrosclerosis. The end stage of the nephrosclerosis due to lead may be very similar to the malignant type of nephrosclerosis. The large vessels of the kidneys show muscular hypertrophy, fraying of the internal elastic fibers and fibrous thickening of the intima. The marked intimal thickening of the small arteries is of hyaline nature. The obliterated vasa afferentia reveal endothelial proliferations. The resulting circulatory changes in the kidneys cause parenchymatous atrophy and interstitial fibrosis. An unusually considerable proliferation of the glomerular capillary endothelial cells together with an accumulation of granular and later homogeneous masses that finally transform the glomerulus into an anuclear material is characteristic of lead nephrosclerosis (Gaylor; Brogsitter and Wodarz; Löhlein; Petri). Occupational lead nephrosclerosis has decreased in frequency in recent years, accord-

ing to Flury, owing to improved working conditions. However, a large number of cases are still placed on record (Vigdortschik; Volhard; Patrassi; Machwitz and Rosenberg; Seiser and Litzner). It may be pointed out that lead nephrosclerosis occurs with and without general hypertension (Teleky; Vigdortschik). Nephrosclerosis in children and juveniles on the basis of chronic lead poisoning sustained during early childhood by eating of lead paint is still rather frequent in Australia (Badham and Taylor; Fairley; Nye; Croll). Nye mentioned renal dwarfism occurring on the basis of lead poisoning in babies.

The renal arterial and arteriolar changes of chronic lead poisoning are sometimes associated with similar lesions in the arteries of other organs, especially the brain (Freifeld; Öller; Staemmler; Rutishauser; Cobb and Blain; Bumke and Krapf; Rühl; Rawkin; Hueper; Petri) in connection with lead encephalomalacia. The cerebral vessels have swollen and proliferated endothelial cells, which often contain lipoid granules apparently originating from the disintegrated nerve tissue nearby, a hyalinized and often calcified media and an edematous adventitial and perivascular tissue containing calcium granules and phagocytic cells loaded with pigment and lipoidal material. The retinal arteries in amblyopia saturnina sometimes reveal hyaline, thickened walls beneath a proliferated endothelial lining. Similar endarteritic changes are observed in the intraneural vessels in lead polyneuritis (Zunker; Eichhorst; Öller). Obliterated arteries in the wall of the stomach and the duodenum (Jores) apparently furnish the anatomic basis of the peptic gastric ulcers not infrequently seen in lead workers on a primary angiospastic basis (Hilka; Peiper; Schiff; von Bergmann; Schüler; Lewin; Badham and Taylor; Glaser). Knapp saw similar endarteritic changes in the mesenteric vessels.

Endarteritic processes leading to gangrene of the ears, the nose, the fingers, the toes and other extremities on the basis of lead poisoning have been reported in workers, many of these in their third decade of life (Baader; Veil; Becker; Kazda; Vigdortschik; Sainton; Decloux; Röpke, Koelsch; Humperdinck; Ribadeau; Dumas; Sabaréanu; Cassierer; Lewin; Lederer; Gerbis; Rutishauser). Flury expressed the opinion that the etiologic relationship of these changes to lead poisoning is not definitely established. Vigdortschik, on the other hand, stated that gangrene of extremities is ten times more frequent in lead workers than in other workers, and Kazda observed lead poisoning in 3 per cent of all cases

of "spontaneous" gangrene of the extremities. Koch also noted that peripheral medial degeneration of the femoral arteries is prominent in lead poisoning, while all other vascular provinces may remain free from disease except for a general thickening of the arterial walls and degenerative changes in the cerebral vessels.

The experimental reproduction of these vascular lesions has been only partly successful. Negative results were observed by Petroff in rabbits and dogs which had inhaled lead tetroxide for a long time. In these animals, after a primary period of normal blood pressure, transitory hypertension developed, followed by hypotension. Similar negative observations were made by Putnoky and Sümegi on rats, which also exhibited transitory hypertension. Fouts and Page, on the other hand, were unable by feeding lead acetate to produce in 2 dogs a hypertensive reaction although the observation period extended over three years and 1 of the dogs died with encephalitis and the usual pathologic changes seen in chronic lead poisoning. Rühl succeeded in eliciting a hypertensive reaction in rabbits by the administration of lead oxide but there were no endarteritic changes in the vessels of these animals. Griffith reported the presence of a hypertensive reaction in 11 of 15 albino rats receiving lead, on the thirty-sixth day of treatment.

Maier, who fed lead to rabbits for ten to twenty-six days, found cellular infiltrations in the adventitia and the media of the aorta, and fatty degeneration in the proliferated media of the small arteries of the stomach and the intestine. Gesenius after eight months of such treatment of 8 rabbits observed fatty degeneration and atrophy of the muscularis of the aorta and the formation of aneurysms. Annino reported that in his rabbits fed lead acetate for six months there occurred severe endarteritic reactions and fatty degeneration of the media. In the aortas of rabbits and guinea pigs Boinet and Romary found plaques of intimal proliferation. Gouget saw in guinea pigs fed lead carbonate severe intimal responses, while Boveri noted aortic aneurysms in rabbits after the administration of lead carbonate. Stieglitz, as well as Jores, recorded the presence of endarteritic changes in the pulmonary arteries of rabbits and guinea pigs which received lead compounds. But Jores, as well as Jores and Haddick, held that these lesions were not comparable to those seen with lead poisoning in man. Annino mentioned endarteritic changes in the small arteries of the intestinal submucosa of rabbits poisoned with lead. Heuben and Rosenstein observed contraction and intimal prolifera-

tions in the cerebral vessels of dogs poisoned with lead but did not see evidence of nephrosclerosis. Eger succeeded in eliciting renal injury in rats by feeding lead, but the lesions were primarily of nephrotic character and not of vascular origin. Philosophow saw in 1 of 3 rabbits receiving lead acetate by injection some foci of medial degeneration and necrosis with thickening of the intima of the aorta. Tscherkess and Phillippowa obtained thickening of the walls of the small arteries of the spleen, the kidneys and the liver in rabbits by chronic lead poisoning.

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*Thyroxin and Iodine.*—Hypertension is a relatively frequent complication of hyperthyroidism (Robinson; Dameshek; Hurxthal; Rosenblum and Levene; Parkinson and Crookson; Parkinson and Hoyle; Maher and Sittler; Bach and Bourne; Crile and McCullagh; DeCourcy; Taussig; Bisgard; McPhedran; Bach and Bourne). The thyrotoxic-hypertensive syndrome has been confused with that present in malignant hypertension, especially as the basal metabolic rate tends to be increased also in nonthyrotoxic hypertensive states. Robinson concluded from the many similarities between hypertension and thyrotoxicosis that the two conditions are etiologically closely related and may represent slightly different manifestations of the same underlying disturbance.

It is usually stated that thyrotoxicosis reduces the tendency toward the development of atherosclerotic vascular changes. Bisgard noted that thyrotoxicosis is either directly responsible for hypertension or, more likely, precipitates or exaggerates a latent vascular disorder, i.e., an inelasticity or restriction of the arteriolar bed such that it is incapable of receiving the normal cardiac output without appreciable elevation in blood pressure. Maher and Sittler expressed a similar opinion when they noted that thyrotoxicosis apparently does not cause cardiac and vascular diseases but brings them to light.

These contentions, however, are not borne out by the not infrequent observation of myocardial necroses and fibroses in patients who died with thyrotoxicosis, as such lesions indicate that relative anoxemia prevails under such circumstances in the myocardium, apparently resulting from the disproportion between the amount of oxygen furnished by the blood and the exaggerated demand for oxygen of the functionally hyperactive heart (Boyksen; Fahr; Wegelin; Rössle; Blastenie; Goodpasture; Lewis; Goodall and Rogers; Loos). These observations in man have been confirmed in experimental animals (cats, rabbits, guinea pigs and rats) treated with thyroid preparations (Hashimoto; Takane; MacEachern and Rake; Menne, Keane and Parade; Menne, Jones and Jones; Boyksen; Heinlein and Dieckhoff; von Zalka; Nora and Flaxman). Similar myocardial lesions in rabbits, guinea pigs and rats followed prolonged administration of sodium iodide (Takane; Radnai and Pilter).

Heinlein and Dieckhoff during the course of their experiments observed that the medium-sized branches of the coronary arteries sometimes revealed severe injury (swelling, splitting of elastica, muscular degeneration) followed by a narrowing of the lumens and moderate perivascular fibrosis. These changes, according to Heinlein and Dieckhoff, are causally related to the myocardial lesions. In confirmation of their observation, moreover, they cited Friedland, as this author reported a sclerosing effect of thyroxin on the blood vessels in general. Kan-Jin-Nan supplied additional support as to the arteriosclerosing action of thyroid hormone, as he observed in rabbits fed thyroid substance necrotic and calcified lesions of the aortic media. Similar changes were observed by von Baló in rabbits after the administration of thyroxin. There appeared first an area of mucoid imbibition of the media with straightening of the elastic membranes followed by calcification. The intima was often markedly fibrous and thickened and showed regenerative elastosis above the medial necrotic foci. Von Baló attributed the arterial necroses caused by thyroxin to the production of an acidotic action. These observations substantiated earlier ones made under similar experimental conditions by Fischer, Murata and Kataoka, Friedland and Kagenova. Von Baló emphasized the practical importance of these observations because thyroxin is often recommended for the prevention and the treatment of hypertension, arteriosclerosis and atherosclerosis.

The same consideration apparently applies to the use of iodides in this respect, as Hedinger and Loeb elicited necroses and calcifications of

the aortic media in rabbits by the subcutaneous introduction of potassium iodide. The mechanism of action of the iodine compound was most likely that of a stimulation of secretion in the thyroid gland.

Brief mention is made of 2 cases in which severe arterial lesions were interpreted as allergic reactions to a chronic intake of potassium iodide (Herzenberg and Maschkileisson). One of the patients, a man 58 years old, had iododerma and generalized obliterative fibrosing and fibrinoid intimal changes with inflammatory destruction of the media in the arteries of the gas-serian and celiac ganglions, the spinal cord, the adrenal glands, the liver, the pancreas and the spleen. Arteries with young lesions showed giant cells in their media which was infiltrated by leukocytes, and thrombotic occlusion of their lumens. In older areas the walls were thickened and fibrous or were converted into giant cell granulomas. In the second patient, a woman aged 47, who had malignant nephrosclerosis, iododerma followed repeated treatments with iodides for a syphilitic infection. The nephrosclerosis, which had been present for four years, was suddenly severely aggravated with the onset of the iododerma.

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**Cold.**—The vasoconstrictory action of low environmental temperature on the vessels of the skin is a well known phenomenon. The chilling of the tissues is said to be followed by an increased release of epinephrine, which elicits this vascular contraction (Hertzman and Roth; Greene). The anoxemia resulting from the reduction in blood flow causes in turn the liberation of a histamine-like substance from the damaged tissue, which produces a secondary local transient vasodilatation followed by a second constrictory phase (Lewis and Love). The main primary effect of cold is swelling of the intima with vacuolation of the media (Smith, Ritchie and Dawson). If tissue is exposed to freezing temperatures, areas of frostbite and finally of necrosis result, which show contracted arteries filled with hyaline thrombi and displaying foci of hyaline degeneration of the media, according to experimental studies on the skin and ears of rabbits and the tails of mice frozen by the application of ether sprays or of salt-ice mixtures (Kriege; Rischpler; Hodara; Greene). Twenty-four hours after the production of the acute ischemic necrosis, multinucleated endothelial cells proliferate into the lumens of the arterioles located in the marginal parts of the affected areas.

Repeated exposures to freezing temperatures in dry air produce chilblain on the hands, the feet, the nose, the ears and other exposed protruding parts and pernio or erythrocyanosis on the legs, affecting particularly the more exposed areas, such as the lower third of the leg, around the internal malleolus and the calf. Pernio may extend down to the dorsum of the foot and the toes and up the legs to the region below the knees. It is found especially in women who wear low shoes and short skirts (Lewis; McGovern, Wright and Kruger; Campbell; Telford and Simmons). It usually disappears with the

onset of warmer weather, to reappear, however, in the fall, indicating thereby the presence of vascular hypersensitivity to cold. In long-standing pernio complete recovery does not occur during the summer because of extensive vascular changes in the tissues. The walls, and particularly the intima, of the small arteries and arterioles in the subcutis are markedly thickened, and the lumens are sometimes occluded. Usually lymphocytic perivascular infiltration and fibrosis are present. Sclerosing and obliterating vascular processes thus represent characteristic features of chilblain and pernio.

Livedo reticularis, a congenital and hereditary anomaly, is another peripheral arteriolar disease of the skin indicating special sensitivity to low environmental temperature. In mild forms the color changes of cutis marmorata are present only during exposures, while in the more severe forms they persist whatever the environmental temperature (Barker, Hines and Craig; Williams and Goodman; Lohnizen; Shumaker; Thomson; Stokes). The available data indicate that a chronic arteriolar spasm is present which ultimately results in the development of endarteritic obliterative lesions. Duryee stated that similar cutaneous reactions have been observed in persons who were exposed to intense heat rays either while standing in front of fires or while sun bathing.

Late effects of vascular injury from cold sometimes manifest themselves weeks and months afterward in the form of gangrene of the extremities due to functional spastic or anatomic obliterative vascular changes (Staehelin; Gruber; Hecht; Jäger; Goecke; Dürck; Röpke; Winiwarter; Erb; Duerdath; Aminjew; Büttner; Bier; Hellmuth; Wieting; Pick; Sonnenburg and Tschmarke; Zoega von Manteuffel; Rudnitski). The histologic character of the arterial lesions is that of endarteritis obliterans or of thromboangiitis obliterans. Wieting witnessed an epidemic of such late effects among the Bulgarian soldiers in the Turkish-Bulgarian War after a cold and wet season. Similar observations were made among former German soldiers who had served in Russia during World War I (Pick; Sonnenburg and Tschmarke). Büttner contended that the cold climate and the excessive use of tobacco are responsible for the extraordinary frequency of thromboangiitis obliterans in Russia. Aminjew made observations among female rope workers in the Ural Mountains who work out of doors during the winter at very low temperatures. Some of these women had gangrenous processes on the fingers and hands which developed on the basis of angiospastic obliterative endarteritic changes. These

observations provide additional evidence supporting the concept that repeated and prolonged vasoconstriction results in sclerosing arterial processes. The vascular injuries accompanying the cold injuries of World War II, namely, immersion foot and shelter foot, will probably be the source of similar endarteritic and gangrenous late results during the coming years (Lake; Ungley and Blackwood; Greene; White; Webster, Woolhouse and Johnston). Ratschow, on the other hand, denied that acrocyanosis and endarteritis obliterans are etiologically related to occupational exposure to cold, as he did not find an exceptionally high incidence of these disturbances among female fishery workers.

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*Physical Trauma.*—The development of an acute and sometimes prolonged or often recurrent angiospasm following a single mechanical trauma to the perivascular tissue with contusion of the vascular wall is a well established fact. Much less definite, however, is the role which such a traumatic angiospasm plays in the subsequent development of arteriosclerotic changes. There are on record some six dozen cases of traumatic segmentary arterial spasm of the main artery and of collaterals of limbs (Kroh; Küttner and Baruch; Viamery; Lacoste and Ferrier; Maury and Daban; Ducastaing; Soubeyran; Cohen; Montgomery and Ireland; de Takáts; Clark; Griffiths; Barnes and Trueta, and others). The final outcome of such an episode of acute ischemia of a limb may be gangrene, ischemic contracture, or complete recovery if the spasm is not too persistent and extensive. Barnes and Trueta succeeded in reproducing these conditions in experiments on rabbits, whose hindlimbs were made ischemic for four and a half hours by the application of a tourniquet. Following the release of the tourniquet, arteriographic studies showed the presence of an angiospasm in the main artery and collaterals of the injured limb. While Clark did not find thrombosis or other gross change in the spastic artery, histologic examinations of such spastic vessels apparently have not been made. It is therefore uncertain whether or not acute anatomic lesions develop in arteries with segmentary spasm.

Contusions of the heart and the cardiac region have given rise to spasms of the coronary arteries resulting in attacks of angina pectoris and in foci of myocardial degeneration, necrosis and fibrosis (Dietrich; Kohn; Leinoff; Gierke; Sigler; Barber; Campbell; Boas; Fischer; Schwach; Thoma). Kastert reproduced such functional coronary and anatomic myocardial reactions in rabbits, which were first exercised on a rotating drum until exhaustion occurred and were then traumatized by a blow with a hammer against

the cardiac region of the chest. Schlomka obtained similar symptomatic results after applying blows to the chests of rabbits and cats. Myocardial lesions, however, were present in only 10 per cent of the animals used. Schlomka concluded that the symptoms were caused by spasms elicited by the direct effect of the vibratory force on the coronary arteries and producing myocardial ischemia. In cases in which acute coronary thrombosis followed the cardiac contusion either a coronary disease was already present or the trauma caused an intimal hemorrhage (Kampmann; Kienle; Schmincke; Meessen; Gronwald). Gronwald, as well as Kment, commented on the medicolegal difficulties connected with adjudication of such cases in compensation courts (Thoma). As atherosclerosis of the coronary vessels is extraordinarily frequent at the end of the second decade of life, causal relations between cardiac trauma and coronary arteriosclerosis are usually not readily apparent unless the changes in the coronary arteries are obviously of recent date. Kohn asserted that repeated traumatic vasospasms of the coronary arteries may ultimately produce organic lesions in these vessels in the form of circumscribed endarteritic arteriosclerosis.

The angiospastic effect of vibratory trauma is most strikingly illustrated in the arterial spasms of Raynaud type in the hands and arms of workers using pneumatic tools such as pneumatic hammers, chisels and drills (miners, stone cutters, foundry workers, riveters, road workers) and lasting machines (shoemakers) (Hamilton; Pfannenstiel; Linow; Linde; Henschien; Fikentscher; Junghanns; Koelsch; Seyring; Teleky; McLaren; Moschinski; Aminjew; Wright; Copeman; Hunt; Meyer-Brodnitz and Wollheim; Gerbis; Holtzmann; Long and Naville; Braencker; Pyro; Kantorowicz; Goecke; Linow; Linde; Meiss; Popken; Ratschow; Rostock; Varshaver, Gladyshevskiy, Ostrovskaya and Stankevich; Beintker; Riesenfeld-Hirschberg; Grotjahn; Schrank). Similar spastic responses are sometimes seen in drivers of tractors, large trucks, motorcycles and bicycles, especially if this work is prolonged and bad road conditions prevail, necessitating a tight hold on the steering mechanism. They are, moreover, occasionally observed in typists, piano players and switchboard operators. The circulatory disturbances consist of numbness, acrocyanosis, paresthesia, anesthesia, coldness, pallor, impaired motility, neuritic pains, decreased temperature of skin, sensitivity to cold and tendency to congelation. Gangrene of fingers has been reported (Holtzmann; Koelsch; Seyring; Teleky). The disease is usually not symmetric and in right-handed

workers usually affects the fingers of the left hand. Junghanns, who is the only investigator who has so far made histologic studies of the affected vessels, noted that the nodular thickenings removed from the arms of one worker revealed arteries with proliferation of the intimal tissue having the character of endangiitis obliterans. The presence or the absence of anatomic vascular changes will most likely depend mainly on the severity and the duration of the exposure and the sensitivity of the patient, as these factors control the occurrence of angiospastic disorders from other causes.

In accidental electric burns, apart from acute coagulation necrosis of the vascular walls (Gordin), the electric current causes vasoconstriction (Lange; Welz; Koeppen; Jellinek; Hüllstrung), which may be followed by vasodilatation subsequent to the development of foci of medial degeneration (Lange). Hüllstrung reported the appearance of attacks of angina pectoris in 3 persons following electric accidents and attributed them to coronary spasms elicited by the electric current. In 2 of these patients angiospasms developed first in the hand through which the current had entered the body. In rabbits Lange demonstrated the presence of medial necroses six days after electric stimulation.

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*Hormones of the Gonads, as Observed at the Climacteric and in Toxemia of Pregnancy.*—

(a) At the Climacteric: In connection with the discussion of the vascular reactions accompanying physiologic processes of senescence ref-

erence was made to the occurrence of cardiovascular disturbances in women and men at the climacteric as the result of imbalances in the secretion of the hormones of the gonads (Bramwell). Scherf, Schaefer and Strassmann called attention to the occasional occurrence of transitory hypertension in women starting with the onset of the menopause and continuing for several years until all climacteric symptoms have subsided. Scherf mentioned that a number of observations speak for the presence of functionally or anatomically narrowed coronary arteries under these conditions. Inasmuch as estrogen exerts a vasodilating effect, the angiospasm with their associated local symptoms (acrocyanosis, migraine) have been related to estrogenic deficiencies (Moffat; Scherf). Other investigators have maintained that these vasospastic conditions are attributable to allergic reactions to estrogenic or androgenic substances (Andresen). On the basis of such observations these substances have been used in recent times with varying symptomatic success in the treatment of hypertension, angina pectoris, thromboangiitis obliterans, Raynaud's disease and related peripheral angiospastic diseases (Walker; Zarrow, Saland, Klein and Goldman; Wagner; Reynolds and Foster; Strong and Wallace; Márquez; Merrmann and McGrath; Edwards).

(b) In Toxemia of Pregnancy: The severe imbalance in the hormones secreted by the ovaries and the hypophysis during pregnancy and the puerperium in the opinion of many investigators determines the production of the hypertension, toxemia and eclampsia of pregnancy and thus is causally related to the acute and chronic degenerative vascular lesions associated with these disturbances. The changes in vascular tonus during pregnancy are accompanied by significant quantitative and qualitative deviations in the composition of the blood. The blood volume, the number of erythrocytes and the lipidal and lipoidal constituents of the plasma are increased, while the serum albumin and therefore the water-binding power of the plasma, as well as the serum calcium, are decreased. These developments are accentuated during toxicosis (Albers; Bodansky and Duff; Dieckmann and Wegner; Hellmuth; Daiser; Stieglitz; Baumann and Holly). The postpartum rise of the blood pressure to levels often considerably higher than those observed during pregnancy, on the other hand, coincides with the onset of lactation and a renewed drop in serum calcium (Adair and Stieglitz). The transitory postpartum hypertensive reaction may be prolonged or exaggerated by the calcium deficiency existing during pregnancy, but it is not considered a precursor to

progressive hypertensive arterial disease starting during pregnancy. In addition to the disturbances of ovarian hormones there occur other endocrine reactions during pregnancy, namely, hyperplasia of the adrenal glands, especially of the cortex (Hofbauer), and proliferation of the basophil cells in the anterior lobe of the pituitary gland and their invasion of the posterior lobe, which is particularly marked in eclampsia (Cushing).

The cause and the causative mechanism of gestational toxicosis with its angiospastic reactions is still highly controversial. Some authors (Cushing; Hofbauer; Küstner; Anselmino and Hoffmann; Fauvet, and others) have claimed that accumulation of the pressor hormone of the posterior lobe of the pituitary gland is the cause of eclampsia. However, in animals repeated and prolonged parenteral introduction of a preparation of this hormone did not produce symptomatic and anatomic responses identical with or even remotely similar to those seen in women with toxicosis of pregnancy (Scheps). Rabbits and guinea pigs thus treated showed contraction only of hepatic and renal arterioles, the contracted and thickened walls of which contained irregularly arranged nuclei. While Hoffmann contended that eclampsia results from overproduction of the cortical hormone of the adrenal gland, Fauvet noted reduced function of this organ. Diel and Erickson tried to link the hypertensive toxemic reactions\* to renal ischemia, as they were able by constriction of the kidneys of pregnant dogs and rabbits to elicit pathologic lesions in the kidneys and livers which morphologically resembled those found in eclamptic women. Similar results were obtained by Dawson, Cressman and Blalock in pregnant dogs after constriction of the renal arteries. Subsequent to the development of hypertension there was widespread renal necrotizing arteriolitis with multiple infarcts, as well as hepatic coagulation necrosis. The hepatic lesions, however, differed from those seen in man and were not associated with hemorrhages and hepatic arteriolar necroses.

Kuepper favored the theory that a combination of protein poisoning (placental infarcts?) with disturbance of the anterior lobe of the hypophysis was responsible for the development of the degenerative and necrotizing parenchymatous renal and hepatic changes and the degenerative and inflammatory arteriolar reactions. Rabbits into which he injected hypophysin and inactivated horse serum died after repeated injections, with round cell infiltration about the afferent renal arterioles, which showed swollen intima. The reactions elicited were of a hyperergic nature and in his opinion were not caused

but merely conditioned by the hypophysin. Inasmuch as identical vascular lesions can be produced by injections of foreign protein alone, the experimental evidence does not support a specific pituitary allergic genesis of eclampsia, but it does not exclude the possibility that at least an allergic mechanism plays an important part in the production of gestational toxemia in view of the anatomic character of the lesions found in eclampsia. Junghans demonstrated an allergic factor which produced in rabbits lesions of the liver and kidneys similar to those in man and which he considered as contributory to eclampsia.

Toxemia of pregnancy apparently starts with a generalized arteriolar spasm, which is responsible for the hypertension (Mussey, Dexter, Weiss, Haynes and Sise; Bartholomew and Colvin; Eastman; Irving; Herrick; Addis). If the angiospasm is not too severe or prolonged, there may be complete functional and anatomic recovery; if it is severe and death ensues, acute sclerotic and necrotic changes in the afferent renal, cerebral and hepatic arterioles may occur in pre-eclampsia and eclampsia (Fahr; Bell; Dexter, Weiss, Haynes and Sise; Heynemann; Page and Cox; Sewall; Irving). In cases in which the eclampsia or the toxemia is not fatal, the hypertensive symptoms may disappear after parturition, either permanently or temporarily, or they may persist, and a malignant renal disease may ensue later. Pregnancies subsequent to a toxemic pregnancy increase the chances of persistent hypertension with each subsequent pregnancy (Williams, Nix and Mauzy; Chesley and Somers). Persistent hypertension with its arterial and arteriolar sclerotic manifestations follows in 25 to 63 per cent of the cases (Corwin and Herrick; Herrick and Tillman; Dieckmann and Brown; Reid and Teel; Peckham). The occurrence of this chronic late sequela apparently depends on the development of anatomic vascular damage during the toxemic episode. The vascular injury, in turn, is dependent in part on the duration of the toxemia. Peckham stated that anatomic vascular changes were present in primiparas who had carried their fetuses for more than twelve weeks after toxemia developed, while the limit in this respect for the multiparas was only six weeks. Chronic vascular damage was observed most frequently in multiparas in whom toxemia was present during the late stage of pregnancy. Although the etiology of the acute and the chronic hypertension of pregnancy is still uncertain, the hypertension nevertheless furnishes an additional illustration of the interrelation existing between angiospasm and the development of acute and chronic arterial and arteriolar necrotiz-

ing or hyalinizing and fibrosing lesions (Golden, Dexter and Weiss) with the probability that allergic reactions play a causal role in the production of the necrotizing reactions.

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#### THROMBOANGIITIS OBLITERANS

Thromboangiitis (or endarteritis) obliterans, or spontaneous juvenile gangrene of the extremities, is an angiospastic disease affecting predominantly males in the third to fifth decades of life (McKittrick). Although exposure to angiospastic agents, such as lead, arsenic, nicotine, ergot and cold, provides in an appreciable number of cases the initiating vasospastic causal factor, the causation in a large number of cases is obscure. Among the important symptoms characterizing this disease are intermittent claudication, rheumatic pain in the affected extremity, decreased temperature of the skin, cyanosis of the extremity when in a lowered position, pallor of the extremity when in a raised position, loss of pulsation of the larger arteries and, not infrequently, migrating superficial phlebitis.

The disease involves most often the lower extremities, less often the upper extremities, and affects in a considerable number of cases also visceral arteries, such as those of the brain, the lungs, the heart, the liver, the mesentery, the intestine and the spermatic cord, thereby assuming a generalized vascular character. Many have observed thromboangiitis obliterans of viscera with or without simultaneous involvement of the arteries of the extremities (Köhlmeier; Meyer; Buerger; Taube; Jäger; Friedmann; Fatheree and Hines; Goodman; Eppinger; Perla; Lehmann; Goecke; Bauer and Recht; Rosenhagen; Stauder; Foerster and Guttmann; Teilum; Saphir; Dürck; Brofeldt; von Dooren; Neusser; Hamburger; Gilbride; Keilty; Antoni; Hueck; Lindenberg and Spatz; Hausner and Allen; Mathé; McGregor and Simson; Staemmler; Kehl and Ritchie; White; Lange; Telford and Stopford).

The marked predominance of males over females among the patients is attested by the fol-

lowing data: More than 99 per cent of all patients with thromboangiitis obliterans are males, according to Telford and Stopford; Buerger saw only 3 women among 500 patients with the disease; Horton noted 21 women among 948 patients whose cases are recorded in the literature; Haga found 1 woman among 34 patients; Dürck noted 1 woman among 6 patients; Koyano recorded 1 woman among 100 patients; Erb reported 7 women among 127 patients; Schlesinger cited a ratio of males to females of 30:1; Horton and Brown a ratio of 9:1, and Wilensky and Collens collected from the literature a total of 24 cases in which thromboangiitis obliterans occurred in the female. Meleney and Miller, as well as Röpke, commented on the rare occurrence of this disease in women and found that its course in women was unusually mild. Horton and Brown suggested that this vascular disorder is probably more frequent among women than generally realized but appears in such a mild form that it is often overlooked. In this connection it may be noted that Kaunitz called attention to the existence of a special susceptibility of the male sex to both thromboangiitis obliterans and the gangrenous form of chronic ergotism. He claimed that thromboangiitis obliterans is a male sex-conditioned, severer form of an angiospastic disease which in its female sex-conditioned, mitigated form appears as Raynaud's disease. Oppel advanced a similar conception when he contended that thromboangiitis obliterans and Raynaud's disease are both caused by hyperadrenalemia (Ornatzki; Achutin; Kosdoba) but that in the male an interaction of androgen with the angiospastic agent accounts for the vasospasm, the injury to the arterial wall and the thrombosis, causing the syndrome of thromboangiitis obliterans, while in the female the interaction of estrogen with the angiospastic agent results merely in angiospastic reactions eliciting the Raynaud syndrome. It is doubtful whether the epinephrine theory of Oppel is correct, as neither thromboangiitis obliterans nor Raynaud's disease is accompanied in most instances by general hypertension such as that present with other forms of hyperadrenalemia. Moreover, Rieder was unable to demonstrate an increase of epinephrine in the blood in 12 of 14 cases of thromboangiitis obliterans. However, vascular lesions similar to those seen in man were elicited in animals when the injection of epinephrine was combined with that of bacterial cultures. Marcus, using rabbits, injected cultures of *Streptococcus* into one ear and epinephrine into the other ear and obtained gangrene in the epinephrine-treated ear, a condition which did not develop when

epinephrine only was injected. Schmidt-Weyland repeated this experiment, using not only streptococci but tubercle bacilli as the sensitizing agent, and saw gangrene appear in 27 of the 67 rabbits thus treated. Injections of epinephrine alone proved to be ineffective.

The vasospastic injury of cold was claimed as the primary or initiating cause of the endarteritic and obliterative vascular reactions by the following observers: Jäger; Goecke; Dürck; Röpke; von Winniwarter; Erb; Gruber; Zoege; von Manteuffel; Rudnistki; Aminjew; Hecht, and others. A lead genesis of the juvenile gangrene of the extremities has been recognized by some investigators (Humperdinck; Gerbis; Koelsch; Vigdortschik, and others), while Röpke, as well as Kazda, noted the occasional occurrence of this disease after lead poisoning. Effects of nicotine occasioned by excessive smoking, especially of cigarettes, plays an important direct or contributory causal role in the opinion of the following writers: Aminjew; Horton; Gruber; Buerger; Lillienthal; Weber; Meyer; Silbert; Assmann; Mendel; Hilpert; Scupham and de Takáts; Lubarsch; Schmorl, and others.

The concept of a specific infection of undetermined character was proposed by Buerger. He attempted to prove this hypothesis by bringing thrombotic material into direct contact with the outside of isolated and ligated superficial veins of the arms of healthy persons and then carefully closing the skin over these implants. In some of the persons thus treated acute obliterative thromboangiitis with giant cell granulomas developed. Allen and Lauderdale, who reported an accidental transmission of thromboangiitis obliterans from man to man through a surgical injury sustained during an operation, held that this incident supported the evidence obtained by work on animals as to the transmissibility of thromboangiitis obliterans by agents probably of bacterial nature. Ceelen advanced the view that a virus might attack either the adventitia or the intima and cause repeated inflammatory stimuli over a period of several years, thus bringing about the complex vascular reactions. He conceded, however, that a prolonged ischemic spasm might facilitate the penetration of bacteria which could cause inflammatory and gangrenous changes subsequent to intimal thickening. Such a mechanism in his opinion is active in the production of cold-induced gangrene. Staemmler, on the other hand, proposed that thromboangiitis obliterans represents a vascular response to the products of tissue degradation and certain reactions of the blood.

A number of observations support the view that an allergic factor is operative in the genesis of thromboangiitis obliterans (Jäger; Scupham and de Takáts; Assmann; Hueck; Rössle, and others). The demonstration of hypersensitivity to nicotine or other fractions of tobacco in an appreciable percentage of persons afflicted with this disease is in favor of this concept. The fibrinoid changes and the inflammatory, particularly the eosinophilic, reactions in the vascular walls furnish additional support. Also in favor of the allergic theory is the fact that thromboangiitis obliterans is not strictly limited to the vessels of the lower extremities but may involve the visceral arteries. Barron and Lilienthal agreed that arteriosclerosis is frequently found in association with thromboangiitis obliterans, even in relatively young patients. Fatherree and Hines, as well as Averback and Silbert, pointed out that the extraperipheral, visceral arterial lesions, while differing from those in the peripheral arteries, are nevertheless related to them. Hueck, as well as Jäger, on the other hand, noted that endangiitis obliterans, although not primarily identical with arteriosclerosis, might ultimately, on long duration, be transformed into this vascular disease. Saphir also emphasized this point.

Brief mention may finally be made of the occasional action of a mechanical traumatic factor in causing the development of thromboangiitis of the arteries of the extremities or of the viscera in apparently predisposed persons (Braeucker; Leriche) who sustained a single acute trauma to the part later affected by the arterial disease.

It is apparent from the list of suspected etiologic factors that angiospastic influences seem to play a significant role in initiating the thromboangiitic process, while chemoallergic or bacterioallergic influences appear to be active in perpetuating, accelerating, accentuating and modifying the initial endarteritic response by superimposing inflammatory, fibrinoid and necrotizing processes. It is in the nature of allergic reactions that they may be locally restricted and thus in this particular instance affect the vessels of certain regions only, or they may be of a more generalized nature. Also significant in this connection is the fact that during the prolonged course of the disease acute exacerbations alternate with long remissions (Saland; Klein; Zurrow; Gootnik and Katz).

An occasional familial occurrence of thromboangiitis obliterans has been observed (Goldflam; Wilensky and Collens; Borchardt; Weiss and Steinberg). It is uncertain, however, whether such observations indicate a genetic factor or

merely a coincidental exposure to the same causal agent.

Claims have been advanced concerning a strong racial factor controlling the development of this vascular disorder. Buerger noted among 500 patients treated in a New York hospital only 4 who were not Jews and contended that Eastern Jews (Poland, Galicia, Russia) were especially susceptible to this disease. This observation was confirmed to a limited degree by others (Braun; Borchardt; Wwedensky; Sternberg; Erb; Kazda; Higier; Goldflam; Idelsohn; Zoege von Manteuffel; Horton). Horton noted that 28 per cent of 948 patients with the disease were Jews. Bier stated that the disease is rare among German Jews but frequent among Eastern Jews, Armenians, Turks and other Eastern peoples (Wieting). Lubarsch reported the disease to be common among the Jews of Estonia. Although the disorder is apparently relatively rare in Germany, Gruber, Helly, Oppel, Redwitz, Ceelen, Jäger and many others observed thromboangiitis obliterans among non-Jews in different parts of Europe. Haga and Koyano recorded its frequent occurrence among the Japanese. Meleney and Miller found it among the Chinese. Eloesser noted that in San Francisco the disease was particularly frequent among Italians and Portuguese. Naide, as well as Yates, observed thromboangiitis obliterans among Negroes.

Inasmuch as Eastern Jews represent a highly complex racial mixture it is not likely that a racial factor plays a role in producing the definite but moderate increase of susceptibility to thromboangiitis obliterans observed in Jews. It is more probable that a limited inbreeding among Jews, occasioned by the special social conditions in the eastern European countries, is responsible for this phenomenon, especially as similar conditions seem to account for the increase of diabetes mellitus and its vascular atheromatous and obliterative gangrenous sequelae among Eastern Jews. These inherited tendencies are possibly aggravated in Russia by the not infrequent exposure to a cold and damp climate and by habitual excess in the smoking of cigarets (Lubarsch; Erb).

Hematic studies on 105 patients with thromboangiitis obliterans showed that the serum calcium, serum protein, blood urea, serum lecithin and serum phosphorus are in general within normal limits (Roth, Maclay and Allen). In most instances the blood volume, the hematocrit value and the concentration of fatty acids and of cholesterol in the plasma were normal. In some instances, however, the blood volume was slightly decreased and the concentration of fatty acids and that of cholesterol were slightly increased. Oppel, as well as Jahsman, Durham

and Dallis, noted polyglobulia in some of their cases. While Oppel concluded from this evidence that there was plethora, Jahsman, Durham and Dallis demonstrated that there was a reduction in plasma volume and thus hemoconcentration. Rabinowitz and Kahn found an increase of the phospholipins of the blood, especially of the cephalin fraction. They related this increase to an increased tendency of the blood toward intravascular clotting and hemolysis in thromboangiitis. Di Cio and Bay, studying 86 patients with peripheral vascular disease, recorded a reduction of the coagulation time in 6 of 10 cases of gangrene of the lower limbs with arterial hypertension, and attributed it to a diminished concentration of heparin and other anticoagulating substances in the blood. Friedlander and Silbert studied the blood in more than 100 cases of thromboangiitis obliterans and noted that the ash content was increased by 30 per cent over the normal level; the total protein content showed a similar elevation; the calcium and cholesterol levels were high normal or moderately above normal, while the volume of the blood was decreased by from 20 to 25 per cent. They concluded from this evidence that there is a process of chronic dehydration in thromboangiitis obliterans. Theis and Freeland observed in their patients deficient oxygenation of the arterial blood and arterial-like oxygen saturation of the superficial venous blood in the involved extremity, in addition to increased viscosity, rapid sedimentation and coagulation, and increased alkalinity. The evidence suggested to Theis and Freeland that there is a disturbance in the utilization of oxygen in acute thromboangiitis obliterans. Jäger noted moderate eosinophilia in several of his cases. The hematic data obtained from various sources suggest the presence of hypoxemic polyglobulia complicated by an increased tendency of the blood to clot in thromboangiitis obliterans, together with blood reactions compatible with an allergic state.

A hypertonic-allergic etiology of thromboangiitis obliterans is not only in harmony with the available information concerning the causal factors and with the symptomatic and hematic findings but also with the complex nature of the anatomic vascular changes. The great complexity and the variability of the histologic lesions seen in thromboangiitis obliterans, which have given rise to markedly differing interpretations as to the nature of the process, are attributable to the fact that three different causative mechanisms are operative in varying intensity in the production of the vascular lesions. A primary angiospastic mechanism is responsible for the endarteritic intimal fibroelastotic proliferations

and the degenerative and fibrosing medial changes extensively present, particularly in the larger vessels (Bunge; Gruber; Ceelen; von Winiwarter; Dietrich; Telford and Stopford). An allergic mechanism is the cause of the inflammatory, fibrinoid and necrotizing reactions seen in these and the smaller vessels. An ischemic hydrostatic mechanism prevails in those parts of the arterial tree which are situated distal to thrombosed or endarteritically occluded segments, and elicits here endarteritic responses. While the two ischemic mechanisms do not produce any distinct disturbances in the structure of the arterial walls, especially no destruction of the internal elastic membrane, the allergic mechanism exerts such an effect, characterized by the appearance of a highly vascularized granulation tissue permeating the intima, the media and the adventitia (Hueck). Mural and occluding thrombi are secondary manifestations.

The granulomatous tissue occluding the vascular lumens either is the result of intimal proliferation or represents tissue formed during the organization and recanalization of a thrombus. It often contains hemoglobinous pigment and giant cells. Lipoidal deposits and calcifications in the walls of such arteries are exceptional. While leukocytes are found in the wall during acute reactions, lymphocytes, plasma cells and histiocytes form the inflammatory exudate during the chronic stages. Eosinophilic leukocytes are often present. The large arteries may present the picture of thromboarteritis ulcerosa, whereas the arterioles may show necrotizing thromboarteriolitis such as that seen in periarteritis nodosa and in rheumatic arteritis, whenever the allergic component of the process predominates. Similar lesions are then found in the accompanying and superficial veins (Buerger; von Wartburg). It is significant that the fibrinoid infiltrations involving mainly the thickened intima are similar to those found in other types of arteriosclerosis associated with infections or intoxication (Jäger). Jäger expressed the view that this fibrinoid material is a product of a reaction between tissues and tissue fluids which is analogous to an antigen-antibody complex. The morphologic changes of the process have the character of a hyperergic reaction, according to Ceelen, who expressed the belief that thromboangiitis obliterans consists of angioallergy to bacterial toxins acting after primary angiospastic injury by cold.

A predominance of the angiospastic component over the allergic one is apparently responsible for a chiefly endarteritic character of the lesions with the thrombotic and necrotic complications remaining in the background (von Winiwarter).

If the latter processes become permanently arrested, the lesions are transformed into scar tissue and assume the character of nodular arteriosclerosis (Hueck; Jäger). Gerlach compared the arterial changes seen in thromboarteritis obliterans with those taking place in the umbilical arteries, where usually ischemic endarteritic changes occur but where occasionally also those of a thromboarteritic character are observed.

The following interpretations as to the character of the disease were placed on these morphologic manifestations: It is a part of the arteriosclerotic complex (Weiss; Bunge; and Zoege von Manteuffel). It is a primary proliferative inflammation of the arterial wall resulting in endothelial proliferation with thrombosis as an accidental by-product (von Winiwarter; Borchardt; Sternberg; Neumann; Goecke; Dietrich; Dürck; Gerlach; von Wartburg; Wilsonski; Gruber). It is an acute specific inflammation of the entire wall of arteries and veins with thrombosis as the main feature (Buerger; Sponheimer; Horton; Nechat; Silbert; Kornzweig and Friedländer; Weber; Boyd). The thromboses develop on the basis of juvenile intimal arteriosclerosis (Weiss; Bunge; Zoege von Manteuffel; Wietung). A primary intimal proliferation of varying genesis represents the characteristic lesion (von Winiwarter; Billroth; Borchardt; von Baumgarten; Sternberg; Schum; Dürck; Goecke; Gruber; Neubürger; Neumann; von Redwitz; Stapf; Wwedensky). The intimal thickenings are the result of proliferation of the elastoblasts, which affects the peripheral small vessels first and extends into the larger arteries (Krompecher). It is obvious that these contradictory interpretations are attributable to the marked variations inherent in the hypertonic-allergic mechanism of the anatomic lesions, to the differences in intensity of the causal components and to the developmental stages of the various vascular reactions.

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## RAYNAUD'S DISEASE

The third of the angiospastic diseases with a pronounced sex-conditioned factor is Raynaud's disease. This affects predominantly women in the age range of 20 to 45. Occasionally it occurs earlier, during the first decade of life, as well as later, after the menopause. However, the symptoms often decrease in severity after the onset of the menopause. Of 204 patients with the disease seen between 1920 and 1931 at the Mayo Clinic, only 2 were girls aged less than 10 and only 1 was a woman above 60. The course of the disease is not influenced by castration (Allen and Brown). The ratio of female to male patients is stated to be 9:1 (White; Horton and Brown). Allen and Brown found males affected in only 11 per cent of their series of 204 cases. The Raynaud syndrome appears in connection with lead poisoning, ergotism, excess of epinephrine, cold, vibration-induced disorders and deficiencies of estrogen (Kaunitz). Bauer noted that the syndrome of acrocyanosis, which combines the vasospastic symptoms of Raynaud's disease with the fibrosing ones of scleroderma, is not uncommon in eunuchoids and cretins, and Galant observed it in connection with female hypogonitalism.

Raynaud, who first described this intermittent spastic vascular phenomenon of the extremities and the protruding parts of the body (nose, ears, cheeks) in 1862 as symmetric gangrene of the extremities, considered it a vasomotor neurosis caused by lesions in the spinal cord giving off abnormal vasomotor impulses. Lewis, on the other hand, asserted from his experimental evidence that it was purely a locally faulty reactivity of the vessels of the extremities to endogenous or exogenous stimuli. This concept received some support from observations made by Hyndman and Wolkin, who studied the effect when the entire body of a nude patient with the exception of a hand was placed in a refrigerator; a vasospastic attack did not occur in the extremity. Simpson, Brown and Adson, however, showed that angiospastic attacks cannot any more be elicited after complete removal of the sympathetic control of the arterioles, thus making Raynaud's disease a true vasomotor neu-

rosis. Clinical observations, moreover, often demonstrate the presence of a psychic factor, as nervous instability is frequently present in patients with Raynaud's disease (Allen and Brown), and minor traumatic insults have played a role in initiating the disease in some persons, apparently through their psychic effects (Lehman; Simon). No case of Raynaud's disease in a Negro has been reported so far (Johnson). There is no general increase in blood pressure, a fact militating strongly against the hyperadrenalism theory of Oppel. Plassmann and Müller, as well as Rieder, held that Raynaud's disease is a disorder of the entire sympathetic nervous system. Both hands and feet were involved in 47 per cent of the 204 cases of Allen and Brown; the hands only were affected in 47 per cent.

During attacks of symmetric angiospasm of the small and medium-sized arteries, the skin first turns dead white and becomes cold, and paresthesias and numbness develop, indicating the effect of anoxia of the tissues. During recovery the waxy pallor gives way first, usually in irregular patches, to a bluish purple to blue-black discoloration and swelling of the tissues. During the final stage the skin becomes red and warm. While the small and medium-sized arteries are functionally obliterated, the pulse in the larger arteries, such as the radial artery, never disappears but may become smaller. Frequent vasospastic episodes may result in superficial trophic changes in the tips of the fingers and the toes. They appear as blisters, keratoses, fissures, depressed scarring of the skin and atrophy and brittleness of the nails. Large necroses involving entire fingers or toes are seen only in old cases (Leriche).

Raynaud's disease is often (10 per cent, O'Leary and Waisman) associated with circumscribed scleroderma of the hands and the feet, giving rise to the syndrome of acrocyanosis (O'Leary; von Notthafft; Gruber; Lewis and Landis; Lewandowsky; Kraus; Saland, Klein, Zurrow, Gootnik and Katz; O'Leary and Waisman; Sellei; Weiss, Stead, Warren and Bailey; Duryee and Wright). Calcareous deposits in the subcutaneous fibrotic tissue have been reported repeatedly (Byron and Michalover; Netherton and Curtis).

It may be mentioned that Lisa and Brown observed a case of Raynaud's disease in which there were endarteritic arteriolar changes in the myocardium, which they considered a part of the angiospastic disease. Linenthal and Linenthal and Talkov noted several cases of Raynaud's disease associated with pulmonary fibrosis and minor sclerotic lesions in the pul-

monary arterioles. Wilkins and Friedland mentioned the association of Raynaud's disease with pulmonary fibrosis and widespread vascular disease, indicating that peripheral angiospasm is a local phenomenon of a more serious systemic disorder.

While it is often stated that Raynaud's disease is not accompanied by endarteritic processes in the intermittently angiospastic vessels, such lesions have been observed repeatedly, especially in advanced and necrotizing forms of the disease. Lewis, as well as Gruber, saw such endarteritic intimal and fibrosing medial changes in the digital arteries of fingers with ulcerations; however, they considered them as nonspecific and as resulting from the adjacent inflammatory processes. This interpretation is not shared by some (O'Leary; Kerr; White; Mufson), who regard them as end results of often repeated spastic ischemia of the vascular walls. It is generally acknowledged, on the other hand, that endarteritic obliterative and fibrosing lesions are commonly present in the cutaneous arteries in connection with acrocyanosis. Although a spastic factor is undoubtedly active in the production of these lesions, an additional ischemic mechanism operates under such circumstances, as the fibrosing changes in the perivascular connective tissue tend to compress the vessels from the outside and to reduce the blood supply needed for the maintenance of the tissues. Hydrostatic factors contribute therefore to the development of the sclerodermic arterial sclerosis.

Rieder cited Hochenegg, Strauss, Schlesinger and others as having observed symptoms like those of Raynaud's disease in association with organic vascular lesions and disturbances of the central nervous system (syringomyelia, multiple sclerosis, tumors of the spinal cord, arteriosclerosis). Changes in the sympathetic ganglions were found in some but not in all cases of Raynaud's disease (Sunder-Plassmann) but, according to Rieder, they are of nonspecific nature since identical inflammatory and degenerative lesions of the ganglions have been observed with various other diseases, such as asthma (Wohlwill) and arteriosclerosis (Staemmler).

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(To Be Continued)

## Notes and News

**Appointments.**—R. D. Baker, associate professor of pathology at Duke University School of Medicine, has been appointed professor and chairman of the department of pathology in the Medical College of Alabama at Birmingham, a division of the University of Alabama, effective on Dec. 1, 1944. Dr. Baker requests that autopsy and surgical materials for the Fungus Disease Registry be sent to him at Birmingham 5, Alabama, after that date. The mycologic and serologic materials for this registry should be sent to Dr. David T. Smith, Duke Hospital, Durham, N. C.

Edward C. Rosenow, who recently became emeritus professor of experimental bacteriology at the Mayo Foundation, University of Minnesota Graduate School, has accepted an invitation to join the California Institute of Technology, Pasadena, to continue with his research.

Edward B. Krumbhaar, professor of pathology at the University of Pennsylvania, has been elected a member of the board of overseers of Harvard University. He has also been elected an honorary fellow of the Royal Society of Medicine, London, in recognition of his distinguished services to science.

**Deaths.**—Israel J. Kligler, who held the Jacob Epstein chair of bacteriology and hygiene at the Hebrew University in Jerusalem, died on September 23 at the age of 55 years.

**Awards.**—Florence Seibert, associate professor of biochemistry at the Phipps Institute of the University of Pennsylvania, has received the medal of the National Achievement Award sponsored by Chi Omega. This medal was awarded in recognition of her outstanding research in tuberculosis.

The gold medal for distinguished service in medicine of the New York Academy of Medicine was presented to Dr. Oswald T. Avery, of the Rockefeller Institute for Medical Research on October 5.

Ernest W. Goodpasture, professor of pathology at Vanderbilt University, was presented with the Sedgwick Memorial Medal on October 3 at the war-time conference and annual meeting of the American Public Health Association.

**Military Program of Clinical Pathologists.**—The plan is to devote a part of the 1945 meeting to subjects of special interest to military pathologists. The meeting will most likely be held in Chicago early next June. It is desired that officers working in the laboratories of military hospitals take an active part in the program. Communications should be addressed to the chairman of the program committee, Dr. A. S. Giordano, 531 North Main Street, South Bend, Ind.

THE ARCHIVES OF PEDIATRICS, published by the American Academy of Pediatrics, is a journal of modern medicine to children. It is devoted to the latest ideas and observations in the field of pediatrics.

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